IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

DEFENDANTS JOHNSON & JOHNSON AND JOHNSON & JOHNSON CONSUMER INC.'S MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE EXPERT OPINIONS OF GHASSAN SAED

DRINKER BIDDLE & REATH LLP
A Delaware Limited Liability Partnership
600 Campus Drive
Florham Park, New Jersey 07932
(973) 549-7000

SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP
1440 New York Avenue, N.W.
Washington, D.C. 20005
(202) 371-7000

Attorneys for Defendants Johnson & Johnson and Johnson & Johnson Consumer Inc.

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

FEDERAL CASES

STATE CASE

OTHER AUTHORITIES

In 2016, after extensive briefing and a multi-week hearing with live testimony, Hon. Nelson C. Johnson of the New Jersey Superior Court rejected plaintiffs' theory of general causation in large part because they did not have credible evidence of biological plausibility – a key consideration in the Bradford Hill framework. As Judge Johnson succinctly explained, "Uttering the term inflammation does not explain the etiology of ovarian cancer . . . ." *Carl v. Johnson & Johnson*, Nos. ATL-L-6546-14, ATL-L-6540-14, 2016 WL 4580145, at *21 (N.J. Super. Ct. Law Div. Sept. 2, 2016), *appeal pending*.

Several months later, plaintiffs' counsel turned to Dr. Ghassan Saed – an associate professor at Wayne State University – in an effort to manufacture biological plausibility for future litigation. Dr. Saed drafted a plan to conduct tests that he expressly predicted would fill this gap in plaintiffs' case. According to Dr. Saed's proposal, his goal was to show that treating cells with talc would cause changes in the balance of certain reactive oxygen species (i.e., the "redox balance"), mutations in certain genes that Dr. Saed claims are associated with ovarian cancer (single nucleotide polymorphisms, or "SNPs"), and – of particular significance – neoplastic transformation (that is, conversion of normal cells to cancer cells). Dr. Saed then conducted some of those tests – but not the test for neoplastic transformation that his own proposal had described as "***critical***" to demonstrating a cause-and-effect relationship between talc and ovarian cancer.

Dr. Saed's litigation-driven experiments were deeply flawed, if not downright fraudulent, and his opinions fail the basic requirements of *Daubert* for a host of reasons.

First, Dr. Saed did not employ reliable methods. Specifically:

- He commenced his work with the expectation that his experiments would achieve the results desired by the lawyers who retained him despite having no prior experience working with talc – revealing a conclusion-driven approach that throws all of his methods into question;

- He did not follow the method he claimed was necessary to show a causal relationship, abandoning several of his plans, including his proposal to test for neoplastic transformation, in favor of indirect and inconclusive alternative testing;

- He did not attempt to use or even identify a dose of talc relevant to human exposure in conducting his studies;

- He did not use valid controls and thus failed to rule out the significant likelihood that factors other than properties unique to talc were driving his results;

- He did not replicate his results in triplicate and thus failed to rule out the possibility that his findings were spurious;

- He relied on improper cell lines – i.e., cancer cells or cells that had been altered so that they could not transform into cancer cells – essentially making it impossible for him to observe transformation from normal cells into cancer cells (the very outcome he ostensibly set out to study);

- He failed to account for results from his genetic studies that made no sense and strongly suggested error, instead asserting that his pre-determined conclusions had been established; and

- He made repeated, egregious errors in his lab notebooks and

> publications concerning fundamental issues such as dose, time of treatment, and basic math, and used white-out and tape to alter his lab notebooks, seriously calling into question the integrity of his work.

Second, Dr. Saed's opinions – even if accepted at face value – fail to establish a plausible biological mechanism by which talc could cause any subtype of ovarian cancer. There is no accepted scientific basis to extrapolate from in vitro petri dish studies to human cancer biology. Thus, at a minimum – as Dr. Saed acknowledged and one peer reviewer expressly commented – Dr. Saed needed to replicate his results in an animal study. He did not do so.

Third, Dr. Saed's opinions are also unreliable because his misrepresentations to peer reviewers reflect a lack of objectivity that is anathema to the scientific method and reliable results. Specifically, Dr. Saed misrepresented the nature of his funding in three separate drafts of his manuscript to two different journals, first failing to acknowledge any conflict at all, then admitting he was paid but not disclosing the fact that lawyers were the source, and then most egregiously (in the published version) denying payment for writing the manuscript when his own sworn testimony expressly states that plaintiffs' counsel paid him for the 60 to 70 hours he expended writing the manuscript. Further corruption of the peer-review process is evident in Dr. Saed's failure to seriously revise his manuscript or reconsider its central conclusions in light of the sweeping criticisms from the reviewers at the first journal that considered and rejected his manuscript for

publication. In fact, it appears that in response to one peer reviewer's apparent incredulity that SNPs were changed following just 48 hours of exposure, he simply changed the manuscript to state that the experiments involved 72 hours of exposure, without changing any of the other data. Of course, fudging the data in this manner is profoundly unscientific, but even if the 72-hour period used in the revised draft were accurate, the result would remain incredible; as Dr. Benjamin Neel, the head of cancer research for NYU Langone, put it: "it's simply impossible" that talc could alter SNPs in a 72-hour period.[1] In short, Dr. Saed subverted the central purpose of the peer-review process – to weed out junk science – by obscuring his funding sources and potentially misrepresenting the data, all in a result-driven effort to obtain the outcome his patrons needed for litigation purposes.

For all of these reasons, discussed further below, the Court should exclude all evidence related to Dr. Saed's experiments, his manuscript and his opinions.

[1] (*See* Dep. of Benjamin Neel, M.D., Ph.D. ("Neel Dep.") 336:17-337:5, Mar. 19, 2019 (attached as Ex. B6 to Omnibus Certification of Julie Tersigni, Esq. ("Tersigni Cert.")).)

BACKGROUND

A. Dr. Ghassan Saed

Dr. Ghassan Saed is an associate professor in the Department of Obstetrics and Gynecology at Wayne State University.[2] As he explained at his deposition, he has never attempted to apply to be a full professor at Wayne State because "[a]pplying for a full professor . . . requires current NIH NCI only funding,"[3] which he last had as a principal investigator in 2012.[4] Plaintiffs' counsel approached Dr. Saed in the middle of August 2017, and he was retained by the end of September.[5]

Dr. Saed, in his words, had "never done anything like" applying talc to cells before he was approached by plaintiffs' counsel.[6] When plaintiffs' counsel contacted him about possibly serving as an expert, he told them that he did not

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[2] (Ex. A at 1-2 to the Expert Report of Ghassan Saed, Ph.D. ("Saed Rep."), Nov. 16, 2018 (entire report including exhibits attached as Ex. C17 to Tersigni Cert.).)

[3] (Dep. of Ghassan Saed, Ph.D. Vol. 1 ("Saed 1/23/19 Dep.") 279:11-17, Jan. 23, 2019 (attached as Ex. B12 to Tersigni Cert.).)

[4] (*See id.* 285:2-23; *see also* Saed Rep. Ex. A at 18.)

[5] (*See* Saed 1/23/19 Dep. 23:12-24:5, 25:2-4, 29:7-10.)

[6] (*Id.* 62:16-23; *see also id.* 27:12-15 (agreeing he had previously done "no studies" involving talc).)

have "any molecular data in [his] laboratory to support the direct effect of talcum powder on [the] markers [he] studied in [his] lab," but he "would like to do that."[7]

B. Dr. Saed's Initial Proposal

Dr. Saed created a "budget" for his experiments – a document entitled, *The role of talc powder exposure in ovarian cancer: mechanist approach* ("Proposal") (Ex. 44 to Dep. of Ghassan Saed, Ph.D. Vol. 2, Feb. 14, 2019 (attached as Ex. B25 to Tersigni Cert.)) – that he shared with plaintiffs' counsel.[8] The document lists three proposed experiments ***and an express and emphatic expectation*** that they will substantiate a link between talcum powder and ovarian cancer and that he would publish the results.

The Proposal had three aims. The first was to "determine the effect of talc on the redox balance in normal ovarian surface epithelial and ovarian cancer cells."[9] Dr. Saed proposed to treat cells with varying doses of talc for 24, 48 and 72 hours and determine what effect these treatments had on certain markers. The second aim was to "[d]etermine whether exposure to talc can induce point mutations that correspond to known SNPs in key oxidant and antioxidant enzymes as well as BRCA1/2, in normal ovarian surface epithelial and ovarian cancer

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7 (*Id.* 275:24-276:21.)

8 (*See id.* 136:5-137:9; Dep. of Ghassan Saed, Ph.D. Vol. 2 ("Saed 2/14/19 Dep.") 497:2-25, Feb. 14, 2019 (attached as Ex. B19 to Tersigni Cert.).)

9 (Proposal at 2 (emphasis omitted).)

cells."[10] Dr. Saed proposed to focus on the BRCA 1 and 2 SNPs and any other SNP implicated by "the results of Aim I."[11] The third aim was to determine whether "[e]xposure to talc results in neoplastic transformation of normal ovarian surface epithelial cells."[12] Dr. Saed proposed to make this determination by "utilizing a neoplastic transformation assay."[13] He also proposed to suspend talc-treated cells in agar and evaluate cell proliferation (i.e., cell growth) and apoptosis (i.e., cell death), comparing the cells to both positive and negative controls.[14]

With all three aims, Dr. Saed predicted success, writing with respect to Aim 3, for example, that "***[w]e expect that exposure of normal ovarian surface epithelial cells to talc will result in neoplastic transformation of these cells over time, which is critical to establishing a cause and effect relationship.***"[15]

C. Dr. Saed's Made-For-Litigation Experiments

Dr. Saed began some of his experiments on September 26, 2017.[16] Notably, Dr. Saed immediately departed from his "aims," most notably by abandoning the

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10 (*Id.* (emphasis omitted).)

11 (*Id.* at 3.)

12 (*Id.* (emphasis omitted).)

13 (*Id.*)

14 (*Id.*)

15 (*Id.*; *see also id.* at 2-3 (similar language with respect to Aims 1 and 2).)

16 (Saed 1/23/19 Dep. 56:9-12.)

neoplastic transformation assay that he had deemed "***critical to establishing a cause-and-effect relationship***."[17]

According to Dr. Saed, he first conducted a number of "pilot studies"[18] to attempt to "tune-up the technique."[19] These pilot studies tested for differences in certain enzyme levels in cells treated with talc and DMSO and cells treated with DMSO only. According to Dr. Saed's lab notebooks, he encountered a number of difficulties. For example, in a lab notebook entry dated October 15, 2017, Dr. Saed reported that he had trouble dissolving talc in DMSO, the solvent he used for his experiments.[20] Another entry, dated January 31, 2018, reported that the concentration of talc being used (1000 µg/mL) was so high that it was "killing the

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[17] (Saed 2/14/19 Dep. 503:10-513:14 (emphasis added); *see also id.* 498:12-499:17, 501:14-502:5.) Dr. Saed insisted that he did conduct part of Aim 3 in that he tested for apoptosis and proliferation. But as he also acknowledged, he tested for apoptosis without suspending cells in agar and used a different cell line from the one he specified in conducting the test (*id.* 506:22-507:7), and the proliferation test he ran was not a neoplastic transformation assay (*id.* 513:9-14). Dr. Saed also did not investigate all the markers he listed in his Aim 1 and omitted SNP testing for the BRCA genes in Aim 2. Dr. Saed denied being "told not to do" what he had proposed (*id.* 502:2-5); indeed, he repeatedly asserted that plaintiffs' counsel had no hand in his study design (*e.g.*, Saed 1/23/19 Dep. 66:20-67:1). But when asked why he did not adhere to his own Proposal, Dr. Saed could only cite "[e]xpenses." (Saed 2/14/19 Dep. 501:25-502:1; *see also id.* 502:22-24, 503:10-19, 505:14-20.)

[18] (Saed 1/23/19 Dep. 57:19-58:5.)

[19] (*Id.* 52:13-22; *see also id.* 56:4-12.)

[20] (Pilot Study Lab Notes at 1 (Saed 2/14/19 Dep. Ex. 23) (attached as Ex. B20 to Tersigni Cert.).)

cells."[21] Nevertheless, Dr. Saed reported findings from experiments using these methods in two abstracts submitted in 2017 and published in early 2018.[22] In neither abstract did he tell the scientific world that plaintiffs' counsel had funded the studies for litigation.[23]

Dr. Saed claims he then turned to the testing conducted for this litigation sometime in early 2018.[24] Although the record is conflicting on exactly how Dr. Saed conducted his experiment, the thrust of it is that he dissolved either Fisher talc or Johnson's Baby Powder in DMSO in three different concentrations; applied those concentrations as well as DMSO only (as a putative "control") to seven cell lines (three ovarian cancer cell lines, two ovarian cell lines, one fallopian tube cell

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21 (*Id.* at 19.)

22 (*See* Fletcher et al., *Talcum Powder Enhances Oxidative Stress in Ovarian Cancer Cells*, 25(Suppl. 1) Reproductive Sciences F-098 (2018) (Saed 1/23/19 Dep. Ex. 20) (attached as Ex. B17 to Tersigni Cert.); Fletcher et al., *LB-044 – Talcum Powder Enhances Cancer Cell Antigen 125 Levels in Ovarian Cancer Cells and in Normal Ovarian Epithelial Cells*, Society for Reproductive Investigation (2018) (Saed 1/23/19 Dep. Ex. 21) (attached as Ex. B18 to Tersigni Cert.); *see also* Saed 2/14/19 Dep. 391:17-392:23.)

23 Because plaintiffs claimed attorney-client privilege over the emails they exchanged with Dr. Saed, a claim upheld by Judge Pisano, the extent of their involvement in the design and conduct of the experiments and the drafting of the manuscript is not easily discernible. (*See* Letter from Susan M. Sharko to Hon. Joel A. Pisano, Jan. 25, 2019 (attached as Ex. G3 to Tersigni Cert.); Letter from Daniel R. Lapinski to Hon. Joel A. Pisano, Jan. 31, 2019 (attached as Ex. G4 to Tersigni Cert.); Letter from Hon. Joel A. Pisano to Counsel, Feb. 5, 2019 (attached as Ex. G5 to Tersigni Cert.).) The inference to be drawn from the privilege claim is, however, obvious.

24 (*See* Saed 1/23/19 Dep. 93:3-7.)

line, and one macrophage cell line); and then ran various tests to attempt to measure enzymatic activity, genetic mutations, and levels of cell proliferation and apoptosis.[25]

The first series of tests he conducted covered some, but not all, of those he had specified in Aim 1 of his Proposal, testing for differences in activity in certain "redox enzymes" – specifically, catalase ("CAT"), glutathione reductase ("GSR"), inducible nitric oxide synthase ("iNOS"), myeloperoxidase ("MPO"), glutathione peroxidase ("GPX") and superoxide dismutase 3 ("SOD3")[26] – that he claims are relevant to the oxidative stress that he believes is a cause of ovarian cancer.[27]

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[25] (*See* Saed Rep. at 13-20.) The details of certain of these steps remain unclear in light of contradictory information in Dr. Saed's lab notebooks and his own testimony. For example, in the first part of his deposition, Dr. Saed testified that he used multiple DMSO controls in varying amounts, one for each concentration of talc that was tested (Saed 1/23/19 Dep. 118:25-119:10), but in the second part of his deposition he claimed that only one DMSO control was used (Saed 2/14/19 Dep. 443:22-446:20). Similarly, although Dr. Saed's report and earlier drafts of his manuscript expressly state that Fisher talc was used in his experiments (*e.g.*, Saed Rep. at 14), Dr. Saed asserted at the second part of his deposition (and in the published version of the manuscript) that only Johnson's Baby Powder was used (Saed 2/14/19 Dep. 541:21-542:9). *See* Fletcher et al., *Molecular Basis Supporting the Association of Talcum Powder Use With Increased Risk of Ovarian Cancer*, Reproductive Sciences 1, 9 (2019) ("Saed Article") (attached as Ex. A39 to Tersigni Cert.).

[26] (SAED000001-97(color) at SAED000012-24(color) (Saed 1/23/19 Dep. Ex. 1) (attached as Ex. B13 to Tersigni Cert.).)

[27] (*See* Saed Rep. at 16-17.) Dr. Saed's Proposal had also indicated that NAD(P)H oxidase, glutathione S-transferase (GST), total glutathione, and 8-OHdG would be included (*see* Proposal at 2), but he did not test for any of them.

Dr. Saed also tested for levels of CA-125[28] – a blood serum marker that is correlated with ovarian cancer progression and treatment response but is not sufficiently sensitive or specific to serve as a reliable indicator of risk for ovarian cancer.[29]

Dr. Saed claims that he next had SNP genotype testing performed by the Applied Genomics Technology Center at the end of June.[30] The ostensible purpose of this testing was to identify gene mutations that Dr. Saed believed might be caused by treatment with talc, but this too was unreliable. While certain genetic mutations (SNPs) are thought to be correlated with cancer, only "SNPs that attain 'genome-wide significance'" – i.e., that are revealed through research to be sufficiently strongly related to cancer risk – "are assured of association with cancer."[31] Dr. Saed's testing focused on specified genes – *CAT* (rs769217), *NOS2* (rs2297518), *GSR* (rs8190955), *GPX1* (rs3448), and *SOD3* (rs2536512)[32] – that

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28 (SAED000035-40(color).)

29 (*See, e.g.*, Expert Report of Jeff Boyd, Ph.D. ("Boyd Rep.") at 8-10, Feb. 25, 2019 (attached as Ex. C22 to Tersigni Cert.); Expert Report of Ie-Ming Shih, M.D., Ph.D. ("Shih Rep.") at 5, Feb. 25, 2019 (attached as Ex. C20 to Tersigni Cert.).)

30 (SAED000078-85(color).)

31 (Expert Report of Benjamin G. Neel, M.D., Ph.D. ("Neel Rep.") at 7, Feb. 25, 2019 (attached as Ex. C10 to Tersigni Cert.); *see also* Saed 1/23/19 Dep. 206:23-207:3 (acknowledging that genome-wide significance means that there is a degree of association sufficient to conclude that a SNP "could be associated with diseases").)

32 (SAED000078(color).)

Dr. Saed claims are relevant to ovarian cancer risk,[33] but ***those genes have never been correlated with ovarian cancer in genome-wide testing***.[34] Some of these genes had been included in Aim 2 of Dr. Saed's Proposal, but other genes that Dr. Saed had specified in the Proposal – including BRCA 1 and 2, which ***have*** been correlated with ovarian cancer risk[35] – were not tested.

Finally, Dr. Saed also conducted tests intended to measure cell proliferation and apoptosis using an MTT cell proliferation assay and a caspase-3 assay.[36] According to Dr. Saed, this testing was intended to serve the same purpose as the testing he had originally proposed in Aim 3,[37] but as he also admitted, testing for cell proliferation and apoptosis is not a direct measure of the "***critical***" endpoint of neoplastic transformation.[38]

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33 (*See* Saed Rep. at 15-16.)

34 (*See* Boyd Rep. at 13-17; Shih Rep. at 7-8.) Dr. Saed resisted this conclusion at his deposition, but could not support the claim that any of these SNPs has been associated with ovarian cancer at a genome-wide level. (*See* Saed 1/23/19 Dep. 207:4-16, 211:6-213:6 (initially identifying only the CAT SNP as being associated with ovarian cancer ***development*** but pointing to literature associating it with ovarian cancer ***survival***); Saed 2/14/19 Dep. 531:15-532:8 (acknowledging that he did not know whether *MPO* had an association with ovarian cancer that has genome-wide significance).)

35 (*E.g.*, Shih Rep. at 3.)

36 (SAED000074-77, 86-87(color).)

37 (*See* Saed 2/14/19 Dep. 508:11-16.)

38 (*See id.* 464:5-17; Proposal at 3 (emphasis added).)

D. Dr. Saed's Lab Notebooks

Dr. Saed ostensibly kept lab notebooks documenting his "pilot" studies and the study underlying his expert report. Specifically, there were two lab notebooks produced in three parts, which will be referred to as follows: the "Abstract Lab Notes," which is a section of one lab notebook that has not been produced in full to defendants and formed the basis for the two abstracts Dr. Saed published in early 2018;[39] the "Pilot Study Lab Notes," which purport to document the "fine tuning" that Dr. Saed claims he did before beginning the experiments underlying his report and comprise the first part of a second lab notebook; and the "Report Lab Notes," which purport to document the work he claims he did for his report and comprise the second part of the same lab notebook in which the Pilot Study Lab Notes were made.

Circumstances and Dr. Saed's own testimony strongly indicate that – contrary to good scientific practice – the lab notebooks were not written until after the fact.[40] When defendants first demanded production of the lab notebooks on December 6, 2018, plaintiffs sought to withhold production until Dr. Saed's

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[39] As the Court knows, Judge Pisano ruled that Dr. Saed should be required to turn over the entire lab notebook for copying, but plaintiffs are appealing that ruling.

[40] (*See, e.g.*, Expert Report of Brooke Taylor Mossman, M.S., Ph.D. ("Mossman Rep.") at 33, Feb. 25, 2019 (attached as Ex. C11 to Tersigni Cert.).)

deposition at the end of January.[41] Judge Pisano ordered them produced at least three weeks prior to the deposition, but plaintiffs further resisted, asserting that Dr. Saed was "out of the country for the holiday" and would "not return to his lab until January 6, 2019," which supposedly made production before January 14 impossible.[42]

In fact, the more likely reason for the delay is that the lab notebooks had not been written – at least not in their entirety, and certainly not contemporaneously with Dr. Saed's work, in contravention of basic scientific methodology. As Dr. Saed expressly acknowledged at his deposition with respect to the lab notebook portion documenting the experiments conducted for his report, "[s]ome of it" was prepared four weeks prior to his deposition,[43] ***precisely when plaintiffs' counsel represented that the lab notebooks could not be produced because Dr. Saed was away for the holiday***. When asked what portion was being prepared during that time, Dr. Saed indicated the last portion of the lab notebook section, a statistical

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41 (*See* Pls.' Steering Committee's Resps. & Objs. to the Notice of Dep. of Ghassan M. Saed, Ph.D. & Duces Tecum at 2-3, Dec. 20, 2018 (attached as Ex. G1 to Tersigni Cert.).)

42 (Letter from P. Leigh O'Dell to Hon. Joel A. Pisano, Dec. 27, 2018 (attached as Ex. G2 to Tersigni Cert.).) When January 14 arrived, plaintiffs produced just one of three sections of lab notebooks that would ultimately be produced (on the dubious ground that the other portions of lab notebooks were not relevant because they reported results from Dr. Saed's pilot studies). (*See* Saed 1/23/19 Dep. 12:19-17:13.)

43 (*Id.* 88:20-22.)

analysis under an entry date of "October 6, 2018."[44] With respect to other entries in the lab notebooks, Dr. Saed claimed to be unable to remember when they were entered and acknowledged that they might not have been entered contemporaneously.[45]

The notebooks also contain entries that make no chronological sense. One striking example is the issue of when the samples that form the basis for all Dr. Saed's experiments supporting his report and manuscript were actually created. Dr. Saed's Pilot Study Lab Notes state that the cells that would be used in his experiments for his report were seeded (i.e., placed in petri dishes for culturing) on February 1, 2018.[46] But his Report Lab Notes state that protein was extracted from the same samples on January 7 or 8, 2018;[47] in other words, the lab notes paradoxically state that Saed was performing tests on samples nearly a month before the samples were even created.[48] In another example, the lab notebook that

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44 (*Id.* 88:23-90:10.) At his deposition, Dr. Saed first testified that the October 6 date indicated when the statistics were run. (*Id.* 90:7-10.) But when it was later brought to his attention that the same statistics appeared in a draft manuscript that he submitted for publication in August 2018, he confessed that he "[couldn't give] the exact date when the statistics were performed." (Saed 2/14/19 Dep. 430:3-431:13.)

45 (Saed 1/23/19 Dep. 88:9-12, 90:11-20.)

46 (Pilot Study Lab Notes at 20.)

47 (SAED000025-28(color).)

48 Dr. Saed confirmed at his deposition that the samples referred to in both sets of lab notes were the same. (Saed 2/14/19 Dep. 389:19-390:17.) Adding to the *(cont'd)*

supposedly recorded Dr. Saed's efforts to "fine tune" his technique conveys that Dr. Saed was having trouble figuring out how to dissolve talc in DMSO on October 15, 2017,[49] while his Abstract Lab Notes report using talc dissolved in DMSO, apparently without issue, on October 7, 2017 – one week earlier.[50]

In yet another example, one entry claims that after Dr. Saed began subculturing cells for testing, the "[c]ells doubled in one day"[51] – which might be possible for the three cancer cell lines that were part of Dr. Saed's experiments, but not for the ovarian or fallopian tube cells, which Dr. Saed acknowledged take "longer"[52] – up to "three, four weeks."[53] Dr. Saed asserted at his deposition that the entry must have been referring only to the cancer cell lines,[54] but the same page of notes indicates that ***all*** cells were subcultured beginning January 26, and two

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confusion, one page of the lab notes indicates that "[c]ells were seeded on 1-3-18" (SAED000025(color)), and the page of the Pilot Study Lab Notes listing February 1 as the date of seeding has a "1/3" date crossed out before "2/1/18" is written (Pilot Study Lab Notes at 20).

49 (*Id.* at 1.)

50 (Abstract Lab Notes at 40 (Saed 1/23/19 Dep. Ex. 9) (attached as Ex. B15 to Tersigni Cert.).)

51 (SAED000002(color).)

52 (Saed 2/14/19 Dep. 422:17-425:15.)

53 (*Id.* 380:10-16.)

54 (*Id.* 424:23-425:15.)

pages after that, the same notes indicate that all cells were treated with talc on February 2 – just a week later.[55]

Notably, a number of entries (including some of those that make no chronological sense) involve the use of white-out – including as to dates in particular – that raise significant questions as to whether the dates and other fundamental facts were entered in the lab notebooks contemporaneously or whether they were instead fabricated much later. For example, the October 7 date just mentioned appears to have been entered originally as 10/17/2017, but the 17 was changed to a 7 by whiting out the "1."[56] Dates both preceding and following it are similarly altered with white-out,[57] making it extremely unlikely that these dates were entered contemporaneously unless the record keeper was wrong about what day it was for more than a fortnight.

White-out was used for other important information as well – indeed, for the very identity of the product being tested. In the Report Lab Notes, for example, the talc identified as being tested is a Johnson & Johnson product, but this information is clearly written over white-out,[58] which Dr. Saed acknowledged at his deposition might have covered up an entirely different product (likely Fisher

55 (SAED000002, 4(color).)

56 (Abstract Lab Notes at 40.)

57 (*See id.* at 39, 41, 44.)

58 (SAED000025(color).)

talc, which is also mentioned in the lab notebooks and early drafts of Dr. Saed's manuscript).[59] Similarly, on one page in the Report Lab Notes, there is a white-out mark and an arrow from the words "Johnson Baby Powder," clearly written after the fact, to a nonspecific reference to "talc" being treated with DMSO.[60]

Dr. Saed's lab notebooks also are missing pages, most notably pages 25 to 29 of the Pilot Study Lab Notes, ostensibly because they related to a different project,[61] but also pages 52, 74, 108-13 and 120 of his Report Lab Notes.[62]

The lab notebooks also contain egregious and inexplicable mathematical errors. In one table that is supposed to report averages of three measurements from his study of GPX, for example, he reports that the average of 2.17, 2.46 and 2.39 is 2.47 – which is obviously incorrect.[63] Dr. Saed could not account for the error at his deposition, saying only that the error was probably a "typo" and that the correct calculation would be "even better" for the conclusions he desired to reach.[64] In another example, Dr. Saed reports miscalculated averages for data on protein activity levels. Specifically, in the first row of a table for talc-treated ovarian

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59 (Saed 1/23/19 Dep. 103:17-104:11.)

60 (SAED000004(color).)

61 (Saed 1/23/19 Dep. 80:19-81:8.)

62 (*See generally* SAED000001-97(color).)

63 (SAED000022(color).)

64 (Saed 2/14/19 Dep. 450:21-451:14.)

cancer cells (from the "A2780-C" line), Dr. Saed lists the average of three values as "11.07" when that value is actually 10.70. When calculating the average for the control cells, Dr. Saed lists an average of three values as 9.13, when, properly calculated, it should be 9.64.[65] Notably, these miscalculations go in the opposite direction from the previous error – i.e., they almost double the difference between the treated and non-treated cells and make Dr. Saed's opinion appear better-supported than it actually is. When confronted with this error at his deposition, Dr. Saed dismissed it as "a very small difference, nothing significant."[66]

Dr. Saed's divergent, results-driven reactions to these errors – happy to correct errors when the correction favors him, but unwilling to acknowledge the materiality of errors that undercut his findings – is profoundly unscientific. And they also miss the broader point: the only way there could be such "typos" in a printed table is if the averages were manually rather than automatically computed, suggesting the possibility of a wide range of "typos" in the other tables that appear throughout Dr. Saed's notes. Notably, plaintiffs' own expert, Dr. April Zambelli-Weiner, asserted in her report that performing mathematical calculations "by hand" instead of using "widely available" computerized methods is "questionable on

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65 (*See* SAED000033(color).)

66 (*See* Saed 2/14/19 Dep. 453:11-24.)

multiple levels" and, where errors result from the manual approach, are indicative of a "lack of validity and reliability" of the work.[67]

Similarly, in another part of his lab notes, Dr. Saed reported a frequency of two allele variants in talc-treated ovarian cancer cells (the "TOV112-T" cell line) as 0.66 for one allele and 0.87 for the other.[68] By definition, these numbers should add up to 1.0, representing 100% of the alleles tested[69] – but the sum of 0.66 and 0.87 is 1.53, or 153%.[70]

In short, Dr. Saed's lab notebooks do not reflect contemporaneous entries and may have been fabricated entirely after the fact. The information they do

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67 (Expert Report of April Zambelli-Weiner, Ph.D., M.P.H. ("Zambelli-Weiner Rep.") at 21, Nov. 16, 2018 (attached as Ex. C8 to Tersigni Cert.).)

68 (SAED000080(color).)

69 (Boyd Rep. at 14.)

70 Dr. Saed's propensity to make what he calls "typos" concerning critical data is breathtaking in scope. In addition to the many "typos" already identified, Dr. Saed testified that literally all of the dose information he provided in his March 2018 abstracts was wrong. In one of them, Dr. Saed wrote that cells were treated with 1000 µg/mL when, according to his testimony, it should have been 100. (Saed 1/23/19 Dep. 317:11-20.) In the other, Dr. Saed wrote that he tested talc in concentrations of 0, 200 and 500 µg/mL when, according to Dr. Saed's testimony, it should have said 0, 20, 100 and 1000. (Saed 2/14/19 Dep. 415:24-417:16.) Similarly, Dr. Saed acknowledged that he misreported the statistical significance of *GPX1* mutation data in A2780 cells treated with 1000 µg/mL of talc in one of his abstract posters – claiming findings were statistically significant when the lab notebooks revealed that they were not. (*Id.* 402:5-406:3.) At his deposition, Dr. Saed downplayed these misrepresentations, testifying that the underlying data clearly indicates that the finding is not statistically significant; but as he acknowledged, the underlying data are not actually presented in the poster, so viewers would not be able to pick up on the inaccuracy. (*Id.* 405:3-18.)

contain is contradictory and inexplicable and riddled with errors and attempts to mask at least some of those errors with white-out and, possibly, removed pages.

E. Dr. Saed's Manuscript

Dr. Saed drew upon these data in drafting a manuscript for publication, entitled *Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer*. Dr. Saed testified that he was compensated by plaintiffs' counsel for the 60 or 70 hours of work that it took him to complete the manuscript – i.e., $36,000-42,000.[71] His first-choice journal – *Gynecologic Oncology*, which focuses on cancer – rejected the manuscript, citing sharp criticisms by two reviewers who viewed Dr. Saed's conclusions as unsupported and asked questions about the interpretation of his results. The second, *Reproductive Sciences* – which does not specialize in cancer – accepted it with little substantive commentary from its assigned peer reviewer.

The initial draft of the manuscript reported that Dr. Saed's lab had treated the cell lines described above with talc for 48 hours and that the authors observed: (1) a dose-dependent increase in pro-oxidants iNOS, nitrate/nitrite and MPO, and a "concomitant decrease" in antioxidants CAT, SOD3, GSR and GPX, in all talc-treated cells; (2) an increase in CA-125 in all talc-treated cells except macrophages; and (3) "an induction of specific mutations in these key enzymes

[71] (Saed 1/23/19 Dep. 33:22-34:9.)

that correlated with alterations of their activities in talc treated cells compared to their controls."[72] Based on these findings, the highlights section submitted with the manuscript asserted that "[o]xidative stress is a key mechanism to the initiation and prognosis of ovarian cancer" and that talc "induces key inflammatory and redox markers" as well as "mutations in key oxidant and antioxidant enzymes," ostensibly demonstrating a mechanism of action by which talc causes ovarian cancer.[73] The draft stated that "[t]he authors have no conflicts of interest to declare"[74] – even though Dr. Saed would be paid tens of thousands of dollars for writing the manuscript itself and had already been paid hundreds of thousands of dollars for a significant part of the same underlying research.

Dr. Saed submitted the manuscript to *Gynecologic Oncology* on August 28, 2018.[75] The submission was rejected. At his initial deposition – before defendants had received copies of his correspondence with the journal, Dr. Saed represented

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72 (Fletcher et al., *Molecular Basis Supporting the Association of Talcum Powder Use with Increased Risk of Ovarian Cancer*, 3. Manuscript at 2 (submitted Aug. 22, 2018) (unpublished manuscript for Gynecologic Oncology) ("Gyn-Onc Manuscript") (attached as Ex. A38 to Tersigni Cert.).)

73 (*Id.* 7. Highlights (for review), at 1.)

74 (*Id.* 3. Manuscript, at 13.)

75 (*See* Email from Gynecologic Oncology to Ghassan Saed, Ph.D. et al. re Gynecologic Oncology: Submission Confirmation (Aug. 28, 2018) (Saed 2/14/19 Dep. Ex. 33) (attached as Ex. B22 to Tersigni Cert.).)

that the reviewers "like[d] it, they love[d] [his] work"[76] and that the only reason it was not published is that the journal had received a "lot of papers" and that Dr. Saed's paper – despite claiming a groundbreaking finding regarding a proposed mechanism in the development of ovarian cancer – simply was "not a priority right now."[77]

But the actual correspondence told a different story. While the rejection letter included boilerplate language regarding the volume of submissions generally, it made clear that the "basis for [the journal's] decision" to reject Dr. Saed's manuscript was set forth in the "attached . . . comments of the [peer] reviewers," who expressed several concerns regarding the content of Dr. Saed's work.[78] The letter further advised: "Please note that a revised version of the current manuscript should not be submitted for another review to Gynecologic Oncology."[79]

The reviewers, though offering encouraging niceties, clearly did not "love" Dr. Saed's work; to the contrary, they viewed it as overreaching and insufficiently supported. The first stated that Dr. Saed's "data are insufficient to back up the

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76 (Saed 1/23/19 Dep. 48:22-49:3.)

77 (*Id.* 49:11-13.)

78 (Email from Gynecologic Oncology to Ghassan Saed, Ph.D. et al. re GYN-18-1020: Final Decision, at 1 (May 19, 2018) ("Rejection Letter") (Saed 2/14/19 Dep. Ex. 35) (attached as Ex. B23 to Tersigni Cert.).)

79 (*Id.*)

claim that talcum is central to the development of ovarian cancer."[80] The reviewer explained that the "data do not show, despite the authors' claim, any evidence that these cells are transformed. Specifically, no experiments documenting changes in cell survival, proliferation or resistance to apoptosis have been performed. Consequently, neither tumor initiation nor progression is documented in this study."[81] The reviewer remarked that "[t]he fact that SNPs were changed following such short exposure to talcum [i.e., 48 hours] is surprising."[82]

A second reviewer raised similar issues with Dr. Saed's conclusion that oxidative stress is a key mechanism to the initiation and progression of ovarian cancer, explaining that his theory "is not supported by this investigation and should be omitted."[83] The reviewer was also skeptical about the "significance of SNP alterations" reported by Dr. Saed and explained that the "cell line studies alone and the increase in CA-125 . . . are not sufficiently convincing."[84]

After being rejected by his first-choice journal, Dr. Saed revised his manuscript and resubmitted it to *Reproductive Sciences*. All references to "48 hours" were revised to "72 hours," even though the experiments reported in the

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80 (*Id.* at 2.)

81 (*Id.*)

82 (*Id.* at 3.)

83 (*Id.* at 2.)

84 (*Id.*)

first, rejected draft were not re-run.[85] When confronted with this discrepancy at his deposition, Dr. Saed claimed that "48 hours is a typo everywhere you see it."[86] But Dr. Saed's "typo" regarding hours of treatment was not limited to his manuscript, reaching also to an abstract that he published before *Gynecologic Oncology* rejected his manuscript and made specific reference to the "surprising" speed of the SNP changes he reported.[87] Moreover, as Dr. Mossman pointed out, "the same data in Figures 1-4 from the *Gynecologic Oncology* submission at 48 hours are now presented using identical Figure Legends 1-4, with the exception that 48 hours has been changed to 72 hours in each Figure legend and on the ordinate of all graphs."[88]

Dr. Saed also added proliferation and apoptosis findings related to his MTT and caspase-3 activity assays, reporting increased cell proliferation and decreased apoptosis.[89] The manuscript also contained a revised conflict of interest disclosure

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85 (Saed 2/14/19 Dep. 487:15-25.)

86 (Saed 1/23/19 Dep. 316:3-12.)

87 (*See* Saed 1/23/19 Dep. Ex. 19 (attached as Ex. B16 to Tersigni Cert.); Saed 2/14/19 Dep. Ex. 31 (attached as Ex. B21 to Tersigni Cert.) (reporting SNP testing results based on treatment time of 48 hours in an abstract based on the same underlying experiments that Dr. Saed submitted to the Society of Gynecologic Oncology's 50th Annual Meeting).)

88 (*See* Mossman Rep. at 32.)

89 (Fletcher et al., *Molecular Basis Supporting the Association of Talcum Powder Use with Increased Risk of Ovarian Cancer* 6, 8 (Jan. 3, 2019) (unpublished manuscript submitted to Reproductive Sciences) ("Reproductive

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that stated that Dr. Saed "acted as a consultant regarding this topic for a fee," without further disclosing the fact that he had been paid in connection with litigation on the same topic.[90]

The editor of *Reproductive Sciences* is Dr. Layman – who works "in the same department and University as Dr. Michael Diamond,"[91] Dr. Saed's former collaborator at Wayne State and frequent co-author. Dr. Layman corresponded with Dr. Saed concerning his submission, including in forwarding the comments of the single assigned peer reviewer of the manuscript. The reviewer asked two questions – "What is the mechanism by which the ovary and not the vagina, the cervix or the endometrium are susceptibles [sic] to talc effects?" and "What do the authors believe is the determining factor for the increased sensitivity of the

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Sciences Manuscript") (Saed 1/23/19 Dep. Ex. 8) (attached as Ex. B14 to Tersigni Cert.).) The draft reported that cells were treated for 72 hours before being tested with the MTT assay, but Dr. Saed's lab book noted only 24 hours of treatment. (SAED000086(color).) At his deposition, Dr. Saed claimed that 24 hours was the right number and that the reference to 72 hours in the manuscript was yet another "typo." (Saed 2/14/19 Dep. 456:17-458:11.)

90 (Reproductive Sciences Manuscript at 12.)

91 (Mossman Rep. at 33.)

epithelial ovarian cells to talc?" – and commented that the manuscript is "wordy."[92]

Dr. Saed made minimal changes to address these comments and other superficial revisions before publication. He also made a slight revision to his conflict disclosure, which now states that "Dr. Saed has served as a paid consultant and expert witness in the talcum powder litigation."[93] But the final draft also added a financial disclosure that states – falsely – that the "author(s) received no financial support for the research, authorship, and/or publication of this article."[94] The article was published in March 2019.[95]

F. Dr. Saed's Expert Report

Dr. Saed's report largely repeats the conclusions of his manuscript; indeed, large portions of it are directly copied. In the report, Dr. Saed asserts that ovarian cancer has been "strongly associated" with inflammation and oxidative stress,

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92 (Email from Lawrence Layman, Editor, Reproductive Sciences to Ghassan Saed, Ph.D., at 2 (Dec. 26, 2018) (Saed 2/14/19 Dep. Ex. 39) (attached as Ex. B24 to Tersigni Cert.).)

93 Saed Article at 9.

94 *Id.*

95 Continuing Dr. Saed's long line of "typos," the published manuscript asserts that Baby Powder was initially "in [DMSO] . . . at a concentration of 500 mg in 10 mL [i.e., ***50 mg/mL***] and was filtered with a ***0.2 µm syringe filter***," Saed Article at 2 (emphases added), in contrast to his Report Lab Notes, which state that a "***10 mg/mL***" solution was prepared, which was "***steriliz[ed] under UV light***" and "***passed 5 times through 22-gauge needle and 0.2 µg syringe filter***." (SAED000004(color) (emphases added).)

although the only article he cites for that proposition discusses a potential link between ovarian cancer and chemoresistance, not risk.[96] To bolster the proposition, Dr. Saed next suggests that ovarian cancer cells exhibit a persistent pro-oxidant state,[97] but he does not address the possibility that it is ovarian cancer that causes a pro-oxidant state, rather than vice versa.[98] This omission is especially striking because some of his own previous work, cited in his report, explained that "tumorigenic cells generate high levels of" reactive oxygen species.[99] In other respects, Dr. Saed generally reports the same findings set forth in his manuscript.

ARGUMENT

Daubert demands that expert evidence comport with the scientific principles that govern experimentation "in a non-judicial setting." *Wade-Greaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1479, 1484 (D.V.I. 1994) (excluding all evidence relating to an experiment conducted for litigation after concluding that the experiment was "not the type that produced scientifically valid data upon which a scientist in this field could reasonably rely" to draw conclusions about causation), *aff'd*, 46 F.3d 1120 (table), 1994 WL 16973481 (3d Cir. 1994); *accord In re Opus*

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96 (Saed Rep. at 4.)

97 (*Id*. at 5.)

98 (*See* Shih Rep. at 28; Neel Rep. at 17.)

99 Saed et al., *Updates on the Role of Oxidative Stress in the Pathogenesis of Ovarian Cancer*, 145 Gynecol. Oncol. 595, 601 (2017) (attached as Ex. A128 to Tersigni Cert.).

E., LLC, 528 B.R. 30, 55 (Bankr. D. Del. 2015) (rejecting expert's cash flow projection opinion because opinions "created by expert witnesses for litigation purposes are inherently suspect"), *aff'd*, No. 15-346-RGA, 2016 WL 1298965 (D. Del. Mar. 31, 2016), *aff'd*, 698 F. App'x 711 (3d Cir. 2017). As discussed in detail below, Dr. Saed's made-for-litigation opinions fail this test because they were driven by litigation at every step and reflect highly unscientific and potentially fraudulent practices.

I. DR. SAED DID NOT EMPLOY RELIABLE EXPERIMENTAL METHODS AND DID NOT GENERATE RELIABLE DATA.

Dr. Saed's experiment departed from bedrock scientific requirements in at least nine ways: (1) he reached predetermined conclusions before he even began his experiments; (2) he failed to follow his own methodological prescription, expressed before the experiment began, that he would need to test for neoplastic transformation to generate data sufficient to support a causal conclusion; (3) he did not attempt to use a dose of talc relevant to human exposure; (4) he failed to exclude other possible causes of his results through the use of valid controls; (5) he failed to run enough tests to support valid conclusions; (6) he relied on cell lines that are irrelevant to determining whether talc exposure causes cancer; (7) he failed to account for inexplicable data that are suggestive of error rather than any causal or biological effect; (8) he failed to keep contemporaneous lab notebooks; and

(9) he made a wide range of errors relating to fundamental issues such as dose and time of treatment in recording and reporting his data.

Any one of these flaws would render Dr. Saed's results unreliable; together, they emphatically establish that his experiment and report are junk science. Notably, a court within this circuit excluded the opinions of another expert who conducted made-for-litigation experiments and committed many of the same kinds of errors and methodological flaws as Dr. Saed. *See Wade-Greaux*, 874 F. Supp. at 1478 (excluding testimony of expert who was "able to draw [her] . . . conclusions only by ignoring the basic requirements of the relevant scientific community's methodology"). In that case, just as in this one, the expert failed to use a relevant dose, to take available steps to confirm findings, to use a sufficiently large sample, to use relevant test subjects, to keep appropriate lab notebooks or to explain extrapolation to human subjects. *See id.* at 1454-55, 1459-61, 1470-71, 1484. And there, too, the experiment was "an essential predicate for [the expert's] opinion," *id.* at 1458, and the serious flaws in the experiment rendered the opinion unreliable and inadmissible. As detailed in the subsections that follow, these circumstances call for the same result.

A. Dr. Saed's Predetermination Of The Conclusions He Expected To Reach Is Contrary To The Scientific Method.

Dr. Saed's methods were tainted from the outset because – as he expressly made clear under each of his three Aims in his Proposal – he came to his conclusions first and then designed experiments to try to prove them.

"Coming to a firm conclusion first and then doing research to support it is the antithesis of [the scientific] method." *Claar v. Burlington N. R.R. Co.*, 29 F.3d 499, 502-03 (9th Cir. 1994). Thus, a "conclusion-driven" analysis is a strong indicator of unreliable methods. *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 798 (3d Cir. 2017); *Snodgrass v. Ford Motor Co.*, No. 96-1814(JBS), 2002 WL 485688, at *12 (D.N.J. Mar. 28, 2002) (rejecting expert who "determined the conclusion before the hypothesis was put forth" and "manipulated the data to achieve a desired result").

In *Claar*, for example, the plaintiffs were employees of Burlington Northern who claimed they had suffered various injuries from exposure to chemicals in the workplace. 29 F.3d at 500. After reviewing the plaintiffs' experts' causation opinions, the district court concluded that they had "formed their opinions before reading the relevant literature, even though they admitted that they were not sufficiently familiar with the field to diagnose the causes of [the] plaintiffs' injuries without first reviewing that literature." *Id.* at 502. The Ninth Circuit affirmed

exclusion of these opinions, explaining that, while "scientists may form initial tentative hypotheses," they cannot form "firm" "conviction[s] about the ultimate conclusion" before conducting their work without losing the "objectivity that is the hallmark of the scientific method." *Id.* at 503.

Dr. Saed's approach here was similarly unreliable. Like the experts in *Claar*, he formed his opinions before he began his work – even though he had no prior experience with talc and therefore had no basis to "***expect***" that his talc-based experiments would produce the highly specific findings he predicted concerning redox balance, point mutations in key redox enzymes and neoplastic transformation.[100] The fact that Dr. Saed prognosticated the success of his experiments is all the more suspect because he deviated from the methods he specified in his original Proposal – strongly suggesting that conclusions, rather than sound methodologies, were driving his work. *Cf. Snodgrass*, 2002 WL 485688, at *12 (excluding expert where circumstances indicated that he tinkered with his methodology until it achieved the desired result). For this reason alone, the Court should exclude Dr. Saed's opinions.

[100] (Proposal at 2, 3.)

B. Dr. Saed Failed To Follow The Method He Claimed Was Needed To Support A Causal Conclusion.

Dr. Saed's experiments and opinions are also unreliable because he did not perform the one test that he said was "***critical in establishing a cause and effect relationship***" between talc exposure and ovarian cancer: "a neoplastic transformation assay."[101] That assay would detect changes from normal cells to cancer cells (if any) and eliminate the need to rely on indirect measures such as cell proliferation, reduced apoptosis or other metrics.

It is axiomatic that an expert who "fail[s] to apply his own methodology" does not satisfy *Daubert*'s reliability requirement. *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 268-69 (2d Cir. 2002) (excluding proposed expert who failed to control for certain variables that he acknowledged needed to be considered); *see also Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 561 (W.D. Pa. 2003) ("Because consistency is a hallmark of the scientific method . . . experts must be required to satisfy their own standards of reliability.") (collecting cases); *cf. Wade-Greaux*, 874 F. Supp. at 1461 (concluding that rabbit study was unreliable in part because its conclusion that Primatene could have caused early embryonic death in some rabbits was based on an inference that was not confirmed through easily available methods of cesarean section or other means).

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101 (Proposal at 3.)

In *Soldo*, for example, the court excluded the plaintiffs' experts' causation opinions as unreliable in part because they "fail[ed] to faithfully apply their own scientific standards." 244 F. Supp. 2d at 560 (capitalization altered). As the court described the approach of one expert, the witness had "explained how one would test the hypothesis that a particular drug causes a specific adverse event," but when asked "whether his causation hypothesis in th[e] case had ever been tested in this manner, he admitted that it had not." *Id.* Another of the experts similarly admitted that the method he used was not the method he had previously stated was necessary to "establish[] causation." *Id.* The court concluded that their opinions were inadmissible, explaining that "their significant departures from their own standards render their methodology scientifically unreliable." *Id.*

Here, too, Dr. Saed failed to do what he himself acknowledged would be necessary to demonstrate carcinogenesis. Prior to starting his experiments, Dr. Saed acknowledged that showing "**neoplastic transformation** . . . utilizing a neoplastic transformation assay" would be "***critical in establishing a cause and effect relationship***" between talc and carcinogenesis.[102] Yet, he never undertook this step.[103] Dr. Saed's failure to "faithfully apply" the very test he claimed was

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[102] (*See* Proposal at 3.)

[103] (*See* Saed 2/14/19 Dep. 465:1-4 ("Q: . . . Have you ever done any tests to look for neoplastic changes in cells directly? A: No").) Dr. Saed claimed that his showing of cell proliferation sufficed to demonstrate an "oncogenic phenotype" *(cont'd)*

"***critical***" to establishing a cause-and-effect relationship further supports exclusion of his opinions.

C. Dr. Saed Did Not Attempt To Use A Relevant Dose.

"In order to reliably opine as to human causation, . . . experts must address" whether doses actually used by humans pose "an increased risk" of the injury at issue. *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 478 (E.D. Pa. 2014); *see, e.g.*, *Bourne ex rel. Bourne v. E.I. DuPont de Nemours & Co.*, 189 F. Supp. 2d 482, 498 (S.D. W. Va. 2002) (excluding expert who relied on a study involving "high-level *in vitro* dosing of cells"). Where in vitro "studies have found associations between exposure and adverse outcomes only at concentrations well above the maximum recommended human dose," the expert lacks a reliable basis for a causal conclusion. *In re Zoloft*, 26 F. Supp. 3d at 478; *see also, e.g.*, *In re Diet Drugs (Phentermine, Fenfluramine, Dexfenfluramine) Prods. Liab. Litig.*, No. MDL 1203, 2000 WL 962545, at *11 (E.D. Pa. June 28, 2000) (excluding two experts, who based their general causation opinions on in vitro animal studies, partially because "the concentration of

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(*see* Saed Rep. at 17) – or, as contended at points in his deposition, that proliferation "is an indirect measure of – of the beginning of a transformation" (Saed 2/14/19 Dep. 464:9-11). As explained in Section II.B however, cell proliferation is not a measure of neoplastic transformation or an "oncogenic phenotype," and even Saed ultimately admits as much.

phentermine used in these in vitro animal studies greatly exceeded any" used in a human clinical dosage); *accord Wade-Greaux*, 874 F. Supp. at 1471, 1480 (concluding that no valid scientific conclusions could be reached from study involving doses that "were two to five times the usual per body weight of what a human could take").

Dr. Saed made no effort to test a dose of talc relevant to perineal talc use. As indicated by Dr. Saed's pilot study, which used talc at such a high concentration that it was "kill[ing] [the] cells,"[104] Dr. Saed had no idea what dose of talc would be appropriate, reflecting Dr. Saed's lack of any prior experience working with talc specifically. *Cf. Wade-Greaux*, 874 F. Supp. at 1459 (noting Dr. Gilbert's limited prior experience working with rabbits specifically). When asked at his deposition whether he could cite "any data showing that the concentrations of exposure that you used in your experiments are similar or the same as would be occurring in women using talc on the perineum," he could only reply, "I can't tell you that."[105] And when further pressed, he expressly acknowledged that his experiment did not replicate human exposure, testifying that

104 (Saed 1/23/19 Dep. 53:9-16.)

105 (Saed 1/23/19 Dep. 232:11-15.)

> the amount of exposure in cell lines, because it's direct and it is an isolated environment, it is definitely not – does not correlate with the in vivo and how much you will get with that exposure.[106]

In short, Dr. Saed did not use amounts of talc in his study that have any relevance to human exposure. For that reason too, the study cannot support an opinion on biological mechanism or causation and should be excluded as unreliable.

D. Dr. Saed Failed To Exclude Other Possible Causes Of His Results Because He Did Not Use Valid Controls.

Dr. Saed also failed to use valid controls. While he sought to control for the effects of talc by treating some cells with DMSO only, he failed to rule out the possibility that DMSO and talc interacted in a way that skewed the results. He also failed to conduct tests with other particulates, such as glass beads, to rule out the possibility that characteristics common to all particulates drove the results of his study, rather than something specific to talc.

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[106] (*Id.* 233:19-23.) In an attempt to solve his glaring dose mismatch, Dr. Saed claimed at his deposition that "there is no minimum threshold beyond which you are protected from developing cancer." (*Id.* 232:24-25.) But Dr. Saed backed away from this opinion just a few lines later, denying that "one particle of talc is enough" and admitting he did not know how much talc was needed to cause cancer. (*Id.* 233:5-10.) In any event, if Dr. Saed is advancing the theory that any exposure to talc, regardless of dose, is carcinogenic, this unscientific theory must be rejected for all the reasons laid out in defendants' Memorandum in Support of Motion To Exclude Plaintiffs' Experts' Opinions Regarding Alleged Heavy Metals & Fragrances In JJCI Cosmetic Talcum Powder at 28-31 and defendants' Memorandum in Support of Motion To Exclude Plaintiffs' Experts' Asbestos-Related Opinions at 89-93.

The use of proper controls is essential to the generation of valid data. *See, e.g.*, *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 276-77 (S.D.N.Y. 2018) (excluding expert in part because he relied on a study for which the control group did not appropriately match his experimental group); *Mancuso v. Consol. Edison Co. of N.Y.*, 56 F. Supp. 2d 391, 403 (S.D.N.Y. 1999) (excluding expert who "did not use a proper control" in her experiment), *aff'd in relevant part, rev'd in part on other grounds*, 216 F.3d 1072 (2d Cir. 2000) (unpub.). That is especially true in this context, where, as noted above, Dr. Saed used large doses of talc to treat his cells, raising the prospect that it was the volume of particulate matter rather than any characteristics unique to talc that were driving his results. *Cf.*, *e.g.*, *Wade-Greaux*, 874 F. Supp. at 1480 ("[A]t some dosage, virtually any substance is teratogenic in an animal species."); *id.* at 1461 (noting that the expert had failed to take steps to rule out other possible causes of growth differences in rabbit pups, and as such, "no one can make a valid scientific finding" based on the results).

Dr. Saed believed that it sufficed to treat some cells with DMSO only and use that treatment as a "control," but this belief was misguided and unscientific in at least two ways. To start, Dr. Saed's apparent assumption that DMSO is neutral and does not itself need to be controlled for is contrary to current scientific understanding. Recent research suggests that DMSO could interact with talc and

"alter the effect that talc would otherwise have on the cells (if any)."[107] Indeed, Dr. Saed's own talc experiments indicate interference by DMSO, since he observed an effect from treatment of cells with supernatant – which is the DMSO with the talc particles removed.[108] Although Dr. Saed ascribed this effect to his inability to "fully isolate the [talc] particles from the supernatant," he did nothing to confirm that hypothesis.[109] For this reason alone, his attempt to control for the effect of DMSO failed, rendering his results unreliable.

Dr. Saed also failed to incorporate proper negative controls such as glass beads, cornstarch or other inert substances to verify that the alleged changes in protein levels and DNA are caused by exposure to talc specifically, rather than exposure to foreign particulate matter generally. Although Dr. Saed dismissed the idea of using a "known inert substance" as a control,[110] he also conceded that he

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107 (Boyd Rep. at 4 (citing Hall et al., *Say No to DMSO: Dimethyl Sulfoxide Inactivates Sisplatin, Carboplatin, and Other Platinum Complexes*, 74(14) Cancer Res. 3913 (2014)).)

108 (Saed 2/14/19 Dep. 393:16-25.)

109 (*See id.* 394:1-8.) It is plain that Dr. Saed did nothing to investigate the suitability of DMSO as a control for his experiment. His lab notebooks reflect the fact that when he first attempted to dissolve talc – whether it was in DMSO or some other medium – it "wo[uld]n't completely dissolve." (Pilot Study Lab Notes at 1.) When asked in deposition why he used DMSO, his answer was incomprehensible, initially stating that he "got this from . . . other papers" and then correcting himself and asserting "we used this DMSO always in our lab to dissolve organic things, nonporous stuff." (Saed 2/14/19 Dep. 433:14-22.)

110 (Saed 1/23/19 Dep. 272:6-12.)

could not rule out the possibility that other particulate matter, such as cornstarch, would have produced the same effect.[111] Notably, at least one study that Dr. Saed referenced at his deposition, a 2009 article by Shukla and colleagues, tacitly acknowledged the importance of using negative controls by incorporating not just talc but also glass beads in its study.[112] Such controls would be necessary here to determine whether Dr. Saed's findings were caused by something unique to talc, or rather by treatment with foreign particles more generally.[113]

Relatedly, Dr. Saed failed to take steps to confirm that the particulate nature of talc would not interfere with the assays he used. Dr. Saed relied on a number of colorimetric assays, which, as Dr. Saed described it, "measure change in color" in order to determine a change in protein activity.[114] But particulate matter can

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111 (*Id.* 273:3-274:25.)

112 *See* Shukla et al., *Alterations in Gene Expression in Human Mesothelial Cells Correlate with Mineral Pathogenicity*, 41(1) Am. J. Respir Cell Mol Biol. 114 (2009) ("Shukla 2009") (attached as Ex. A131 to Tersigni Cert.). While Dr. Saed suggested that Shukla's study was supportive of his conclusions (*e.g.*, Saed 1/23/19 Dep. 339:23-340:15), that study noted that "nonfibrous talc is regarded as noncarcinogenic in humans," Shukla 2009 at 119, and found that after 24 hours, talc treatment did not induce any changes in mesothelial cell mRNA and that it did not induce any mRNA changes at any time in ovarian epithelial cells, *id.* at 120.

113 (*See also, e.g.*, Boyd Rep. at 6-7 ("[E]xperiments testing the potential biological effects of other particulate compounds like talc could have been used to determine whether [Dr. Saed's] findings were driven by some quality that is unique to talc, or rather its particulate form generally."); Mossman Rep. at 31 (similar).)

114 (Saed 2/14/19 Dep. 435:2-436:1.)

interfere with the measurements taken in colorimetric assays and skew their results.[115] Dr. Saed did not deny this proposition at his deposition, instead insisting that his lab was able to wash all talc off of cells before they were tested in the assays.[116] But Dr. Saed's lab notebook acknowledges that "[l]ysate protein measurements may be affected by talc. Repeat protein measurements, have control w/ talc in it."[117] And he offered no evidence supporting his assertion that the techniques he used to "wash" cells of all talc prior to testing were failsafe.

In short, because Dr. Saed has not ruled out the possibility that his findings are non-specific to talc or that they resulted from talc's interactions with DMSO, his study design is unreliable, and his opinions must be excluded for this reason as well.

E. Dr. Saed Failed To Run Sufficient Tests To Demonstrate That His Results Were Reproducible.

Dr. Saed also failed to demonstrate that his results were reproducible. Reliable science generally requires that experiments like Dr. Saed's be run in triplicate to show that the results are not spurious. Here, Dr. Saed claimed that he performed the experiments three times, but in reality, all he did was measure the

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115 (Report of H. Nadia Moore, Ph.D., D.A.B.T., E.R.T. at 93, Feb. 25, 2019 (attached as Ex. C19 to Tersigni Cert.).)

116 (Saed 2/14/19 Dep. 439:21-441:19.)

117 (Pilot Study Lab Notes at 15.)

effects in the same sets of treated cells three times. This is not what is meant by running an experiment in triplicate.

An expert should not be permitted to testify on the basis of experiments that he or she has not sufficiently reproduced, and the failure to reproduce findings is especially glaring when the experiment is plagued by other methodological issues. *See Rovid v. Graco Children's Prods., Inc.*, No. 17-cv-015606-PJH, 2018 WL 5906075, at *5 (N.D. Cal. Nov. 9, 2018) (excluding an expert's opinion in part because he only ran a single test, and "[w]ithout multiple tests, [the expert] cannot show that his results are reproducible or reliable"); *Koch v. Shell Oil Co.*, 49 F. Supp. 2d 1262, 1268 (D. Kan. 1999) (excluding expert in part because "he did not make duplicate or triplicate runs of the final experiments"); *accord, e.g.*, *Wade-Greaux*, 874 F. Supp. at 1460 (concluding that "too few animals were used in too many dosage groups" to produce sufficiently robust results to provide a "scientifically valid basis for identifying causal relationships"). Dr. Saed apparently agrees that replication should be required, as his proposal indicated that "[a]ll experiments w[ould] be performed in triplicate."[118] Indeed, he ***still*** claims that the he performed his experiments in triplicate.[119]

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118 (Proposal at 4 (emphasis omitted).)

119 (*See* Saed 1/23/19 Dep. 123:2 ("Every experiment is done in triplicate").) *See* Saed Article at 4 fig. 1 (claiming that "[e]xperiments were performed in triplicate").

But despite his protestations to the contrary, Dr. Saed ***did not perform his experiment*** in triplicate. Rather, he plated ***one*** dish of each cell line all at the same time and then treated all of them, all at the same time. He then ***measured his results*** three times. This is not an experiment in triplicate.[120] Rather, it is a single experiment that has been measured three times. Even Dr. Saed eventually acknowledged as much, explaining that in some of his other work he has done "real triplicate," but in this experiment he merely did "triplicate of the assay."[121] The difference is critical, because the purpose of a replicated experiment is to control for the possibility of unique conditions that might produce abnormal results. *See Avon Prods., Inc. v. S.C. Johnson & Son, Inc.*, 984 F. Supp. 768, 787 (S.D.N.Y. 1997). Since such conditions can happen at any point in the experimental process, repeating one small portion of the process (in this case, the measurement step) multiple times does little to reduce such a risk.

In short, Dr. Saed's admission that he did not perform experiments in "real triplicate" – contrary to his express claims that experiments were performed in triplicate – further renders his experiment and the opinions derived from it unreliable and inadmissible.

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120 (Mossman Rep. at 33 ("He also states in every figure legend that '[e]xperiments were performed in triplicate,' when in fact his testimony and notebooks show that this is false.") (citation omitted).)

121 (Saed 1/23/19 Dep. 127:4-8.)

F. Dr. Saed Relied On Irrelevant Cell Lines.

Dr. Saed also studied cell lines that could not possibly support his conclusions on biological mechanism and causation because they were cells of irrelevant origin, immortalized (meaning they could not be transformed into cancer cells), or were already cancer cells (meaning they obviously could not show how talc could ostensibly transform normal cells into cancer cells).

Multiple courts have held that an in vitro study cannot be used to demonstrate in vivo causation unless it is performed on normal human cells from the target organ. *See, e.g.*, *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 429-30 (S.D.N.Y. 2005) (excluding expert who relied on "liver cells of rats, cancerous human liver cells, and cancerous or otherwise abnormal cells from other human organs" in an attempt to show effects on healthy human livers); *Mancuso*, 56 F. Supp. 2d at 403 (excluding expert who relied on immortalized cell lines, noting they were particularly inappropriate to show carcinogenesis); *cf. Wade-Greaux*, 874 F. Supp. at 1460 (excluding rabbit study as unreliable in part because it had used rabbits past their prime fertility age in a study that was attempting to demonstrate effects on fertility). Of particular significance, as the *Rezulin* court pointed out, tests on cell lines from the wrong organ, or on cell lines that are from the same organ but are different from normal cells with respect to the mechanism under study, cannot form the basis for reliable extrapolations. 369 F. Supp. 2d at

430 (non-liver cells and cancerous liver cells in a study focused on alleged injury to healthy liver cells).

Here, Dr. Saed used several cell lines, all of which were improper for his research purpose. The EL-1 cell line he used consists of macrophages derived from the human spleen, which is the wrong organ, and no explanation was provided for his use of these cells. The other cells were ovarian or fallopian tube cells, but all of them were already cancer cells or had been altered so that they could not transform into cancer cells. Specifically, the fallopian and ovarian epithelium cells Dr. Saed used were "immortalized." As Dr. Saed admitted, he could not show transformation of these cells to cancerous cells because immortalized cells "do not transform," and therefore could not provide relevant information about the relevant endpoint here (i.e., whether talc causes normal cells to transform into cancer cells).[122] Finally, Dr. Saed also used "ovarian cancer" cell lines SKOV-3, A2780 and TOV112D,[123] but effects observed on cells that are ***already cancerous*** plainly cannot establish the mechanism by which normal cells develop into cancer cells in the first instance. Moreover, "none of the three 'ovarian' cancer cell lines used were derived from high-grade serous carcinoma,

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[122] (Saed 2/14/19 Dep. 464:13-17; *see also id.* 464:22-25 ("[T]he normal [cells] we used are immortalized cell lines. That means they do not change unless you really beat them up.").)

[123] (Saed Rep. at 13.)

which is the most common histological subtype of ovarian cancer and the disease focus of several of plaintiffs' epidemiology experts in this litigation."[124]

In short, Dr. Saed seeks to opine on the effects of talc on normal ovarian or fallopian cells, but he did not test a single such cell. This is precisely the error made by the purported experts in *Rezulin* and *Mancuso*, and Dr. Saed's testimony should be excluded for the same reason.

G. Dr. Saed Failed To Account For Inexplicable Results From His SNP Analysis That Strongly Suggest Error Rather Than Causal Or Biological Effect.

Dr. Saed's conclusions regarding his SNP data are also unreliable. Dr. Saed assumes that the results indicate that talc exposure caused mutations. But the results make no sense: some cell lines and genes exhibited no mutations at all, and the allele frequencies are mathematically impossible in some instances and inexplicable in others. Combined with the fact that, for Dr. Saed's theory to hold together, talc would need to produce mutations in 48- or 72-hour periods – an impossibly short timeframe as a matter of basic science, especially in non-cancer cells – the most plausible explanation for Dr. Saed's results is error.

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[124] (Shih Rep. at 6.) Although the cell lines Dr. Saed used were, at one time, frequently used ovarian cancer models, recent evidence shows that they are "not representative of ovarian cancer," a fact about which Dr. Saed appears to be unaware. (*See* Neel Dep. 350:13-351:10.)

Although the Court's *Daubert* analysis focuses on methodology rather than conclusions, methodology and results "are not entirely distinct from one another." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). Thus, an expert's opinion is likely to be inadmissible if his or her methodology produces "nonsensical" or otherwise difficult-to-comprehend results. *In re LIBOR-Based Fin. Instruments Antitrust Litig.*, 299 F. Supp. 3d 430, 501 (S.D.N.Y. 2018) (concluding that the expert's method produced "nonsensical results," indicating a "high potential rate of error," and excluding it as unreliable); *In re TMI Litig.*, 193 F.3d 613, 683 (3d Cir. 1999) (excluding expert opinion that produced results that "fl[ew] in the face of reality"), *amended in nonmaterial part*, 199 F.3d 158 (3d Cir. 2000); *accord Wade-Greaux*, 874 F. Supp. at 1459-60 (excluding opinion based on experiment in which, paradoxically, malformation was found with low-dose treatment, but not high-dose treatment).

Here, Dr. Saed's interpretation of the SNP data is wildly unscientific and irreconcilable with fundamental biological principles. To begin, the notion that talc – or anything – could induce mutations in such a short timeframe is scientifically unsupported. Dr. Saed essentially agreed, testifying that he "[could] []not recall" any other substances that have been reported to cause the types of

mutations he reported after 72 hours of treatment cell culture.[125] That is because it does not happen. Mutations typically occur as a result of DNA copy errors; and copying only occurs when a cell divides.[126] As Dr. Saed acknowledged at his deposition, normal epithelial ovarian cells take "like a week to grow" – they are "very slow-growing cells."[127] Yet, Dr. Saed represented in his submissions to *Gynecologic Oncology* and *Reproductive Sciences* that talc had produced mutations in his normal ovarian cells ***in just 48 or 72 hours respectively*** – well short of a week in either event, and not nearly enough time for cells of one genotype to be replaced by cells of another, by Dr. Saed's own admission.[128]

To the extent Dr. Saed instead means that talc somehow induced genotype switches within the same cell within 48 or 72 hours, without the need for copying errors through cell division, there simply is no scientific or biological basis for such an assertion. As Dr. Neel put it, the "wholesale change in [the] genetic content of a specific . . . SNP within 72 hours . . . would be utterly unprecedented as far as I know in molecular biology" – "like finding a needle in a haystack and turning the needle into a hammer."[129] Consistent with these scientific realities, the

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125 (Saed 1/23/19 Dep. 252:3-7.)

126 (*See* Boyd Rep. at 14.)

127 (Saed 2/14/19 Dep. 423:19-24.)

128 (*See id*.)

129 (Neel Dep. 369:10-17, 337:3-5.)

reviewers of *Gynecologic Oncology* expressed doubts about Dr. Saed's claim in the letter refusing to publish Dr. Saed's manuscript: "The fact that SNPs were changed following such short exposure to talcum is surprising . . . ."[130]

Other data in Dr. Saed's SNP results should have alerted him to the fact that something was not right. The minor allelic frequencies he reports, for example, simply do not work as a matter of basic math. As Dr. Boyd noted in reviewing his work, the "Allele Amp Scores" recorded in Dr. Saed's lab notebook for the two allele variants of the rs768217 mutation in talc-treated TOV112D cells were 0.67 (C/C allele) and 0.88 (C/T allele allegedly induced by talc treatment),[131] meaning that 67% of the alleles were the C/C variant while 88% were the C/T variant. The combined frequency of these allele variants, therefore, would add up to 155%, even though the combined frequency must total 100%.

Moreover, the mutagenic potential Dr. Saed infers from his results lacks coherent support from those same results, only some of which reported a "genotype switch." For example, neither the rs769217 SNP, which occurs in an

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130 (Rejection Letter at 3.) The other reviewer expressed confusion in indicating similar doubts, writing, "The significance of SNP alterations should be further clarified." (*Id.* at 2.) The fact that the reviewers of *Reproductive Sciences* offered no similar objection is immaterial. *Reproductive Sciences* is not a cancer journal, and its reviewers likely lack the expertise needed to understand the impossibility of what Dr. Saed is reporting. (*See* Neel Dep. 337:6-19.)

131 (Boyd Rep. at 14.)

area that codes for the *CAT* enzyme, nor the rs2297518 SNP, which occurs in an area that codes for the *NOS2* enzyme, was found in two of the three ovarian cancer cell lines that Dr. Saed tested.[132] Dr. Saed offers no explanation for why, if he were really observing a mutagen so potent that it induced changes in 72 hours, he would find mutations in some cell lines but not others.

Finally, Dr. Saed made no effort to try to reconcile the conclusions he drew from his flawed SNP data with preexisting literature, which has roundly rejected the notion that talc is genotoxic. Where there is a body of contrary evidence, an expert must, at the very least, address it and explain his or her reasons for departing from it. *See Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 882 (10th Cir. 2005); *see also, e.g.*, *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 461 (E.D. Pa. 2014) (excluding expert that "fail[ed] to account adequately for contrary evidence"); *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, No. 12-md-2342, 2015 WL 7776911, at *7 (E.D. Pa. Dec. 2, 2015) ("Scientists are expected to address and reconcile data that does not support their opinions, and not simply rely upon data which does."); *In re Rezulin*, 369 F. Supp. 2d at 425 ("[I]f the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable.").

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[132] (*See* Saed Rep. at 18-19; *see also* Reproductive Sciences Manuscript at 19.)

Here, well-performed experiments published in the literature for decades have repeatedly and consistently shown that talc is not genotoxic,[133] does not increase cell survival or proliferation in rodent cells[134] or otherwise cause cancer,[135] and does not change gene expression.[136] Consistent with this literature, the recent meta-analysis performed by Mohamed Taher and others in an unpublished manuscript on which plaintiffs' other experts rely also asserted unambiguously that talc is not genotoxic.[137] And talc is injected into the cavities

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133 *See, e.g.*, Endo-Capron et al., *In Vitro Reponses of Rat Pleural Mesothelial Cells to Talc Samples in Genotoxicity Assays*, 7(1) Toxicol. In Vitro 7 (1993) (attached as Ex. A32 to Tersigni Cert.).

134 *See* Wylie et al., *Mineralogical Features Associated with Cytotoxic and Proliferative Effects of Fibrous Talc and Asbestos on Rodent Tracheal Epithelial and Pleural Mesothelial Cells*, 147 Toxicol. Applied Pharmacol. 143 (1997) (attached as Ex. A156 to Tersigni Cert.); Stanton et al., *Relation of Particle Dimension to Carcinogenicity in Amphibole Asbestoses and other Fibrous Minerals*, 67(3) J. Nat'l Cancer Inst. 965 (1981) (attached as Ex. A136 to Tersigni Cert.); Smith et al., *Biologic Tests of Tremolite in Hamsters*, Dusts Disease 335 (1979) (attached as Ex. A135 to Tersigni Cert.).

135 Hamilton et al., *Effects of Talc on the Rat Ovary*, 65 Br. J. Exp. Pathol. 101 (1984) (attached as Ex. A53 to Tersigni Cert.); Keskin et al., *Does Long-Term Talc Exposure Have a Carcinogenic Effect on the Female Genital System of Rats? An Experimental Pilot Study*, 280 Archives Gynecol. Obstet. 925 (2009) (attached as Ex. A85 to Tersigni Cert.).

136 Hillegass et al., *Utilization of Gene Profiling and Proteomics to Determine Mineral Pathogenicity in a Human Mesothelial Cell Line*, 73(5) J. Toxicol. Envtl. Health A 423 (2010) (attached as Ex. A64 to Tersigni Cert.); Shukla 2009.

137 *See* Taher et al., *Systematic Review and Meta-Analysis of the Association Between Perineal Use of Talc and Risk of Ovarian Cancer*, at 41 (2018) (unpublished manuscript) (attached as Ex. A137 to Tersigni Cert.) ("[R]eview of

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surrounding the lungs in pleurodesis, but studies have found no increased rates of cancer among pleurodesis patients, further suggesting that talc is not genotoxic. Dr. Saed not only fails to explain why he discounts this evidence; he does not even mention it at all. For this reason, too, his unscientific opinion must be excluded.

H. Dr. Saed's Lab Notebook And The Work Derived From It Are Rife With Errors.

Finally, Dr. Saed's work is full of other errors, contradictions and obfuscations, beginning with his lab notebook and extending to all work derived from it, including his manuscript and report.

As noted above, the lab notebook is full of unexplained alterations – including the repeated use of white-out – that appear intended to obscure its original contents.[138] It contains basic mathematical errors that indicate that calculations that would be performed by computers in the ordinary course must have been done by hand – a practice plaintiffs' own expert criticizes as

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evidence exploring in vitro and in vivo toxicology data" "indicates that talc is not genotoxic.").

[138] As Judge Pisano noted in ordering Dr. Saed to produce a complete copy of one of his lab notebooks, Dr. Saed "was shown to be less than forthcoming in his production of laboratory work materials, he was found to have altered laboratory notebook entries, [and] he combined, incorporated, or commingled notes from different studies in the same notebook." (Letter Op. from Hon. Joel A. Pisano to All Counsel of Record at 3, Apr. 26, 2019 (attached as Ex. G6 to Tersigni Decl.).)

unreliable.[139] And as already mentioned, other data in the lab notebook, such as the frequencies reported for some alleles in the SNP testing, literally do not add up. Similarly egregious errors manifest themselves in the formal presentations of Dr. Saed's purported results. While his report and manuscript are essentially one and the same at this point, they contradict treatment times claimed by Dr. Saed in prior drafts of the manuscript and in abstracts arising out of the same work.

Scientific evidence that is "not reported in an accurate manner" should be excluded. *Louis Vuitton Malletier v. Dooney & Burke, Inc.*, 525 F. Supp. 2d 558, 569 (S.D.N.Y. 2007) (citation omitted) (excluding experts whose survey-research-based opinions were riddled with error); *Wade-Greaux*, 874 F. Supp. at 1460 (highlighting that one problem with the excluded rabbit study was inconsistencies between lab book and expert report concerning fundamental but simple data such as the number of rabbits tested). While the occasional error in an expert's work generally goes to the weight of the evidence, an expert's opinions cannot be admitted where the underlying data and analyses are "so flawed as to be completely unhelpful to the trier of fact." *Louis Vuitton*, 525 F. Supp. 2d at 563 (citation omitted).

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139 (Zambelli-Weiner Rep. at 21.)

This is such a case, because Dr. Saed's lab notebook and derivative work are so flawed that it is impossible to know what he did or what actual results he obtained. For example, and as detailed in the Background section above:

- Dr. Saed's manuscripts misreported the time of treatment by half – reporting 48 hours of treatment when (he claims) the cells had actually been treated for 50% longer (i.e., 72 hours total). This error is especially striking and significant because the shortness of time in which Dr. Saed believes he observed mutations "surpris[ed]" one of the reviewers in Dr. Saed's rejection letter from *Gynecologic Oncology*;

- Dr. Saed's abstracts repeatedly misreported the doses of talc that he tested, which is also of tremendous significance in light of the critical role dose plays in toxicity and Dr. Saed's own experience, which revealed that higher doses of talc were "killing the cells";

- Portions of the lab notebook are whited-out with different – frequently contradictory – information written over the original, whole pages have been ripped out and the missing information not explained or accounted for, and sections of data have been physically cut from one page and taped onto a different page;

- Dr. Saed's work contains basic and fundamental mathematical errors that suggest his data were computed by hand and render the fundamental underpinnings of his findings unreliable; and

- Even the ***identity of the product Dr. Saed tested*** is unclear. His draft manuscript claimed it was Johnson's Baby Powder and Fisher talc, but his lab notebook has "Johnson & Johnson" written over white-out, and Dr. Saed conceded that it was entirely possible that Fisher talc had been written underneath the white-out.

These errors make it impossible to establish the reliability and scientific validity of Dr. Saed's broader conclusions about the biological effects of talc on protein activity, DNA mutations and cancer induction. Of equal importance is

Dr. Saed's nonchalance toward these errors, which evinces a shocking indifference to the validity of his methods. Under these circumstances, the Court can have no assurance that Dr. Saed's work adheres to the level of rigor required by the standards in his field. For this reason, too, the Court should exclude Dr. Saed's opinions.

II. EVEN IF DR. SAED'S FLAWED EXPERIMENT HAD PRODUCED RELIABLE DATA, THOSE DATA WOULD NOT SUPPORT HIS CONCLUSIONS.

Dr. Saed's opinions are unreliable and inadmissible for an additional and independent reason: his data, even if otherwise reliable, do not support his conclusion that talc is carcinogenic.

An expert opinion, even if reliable, should be excluded if "there is simply too great an analytical gap between the data and the opinion proffered." *Joiner*, 522 U.S. at 144, 146 (excluding experts who "extrapolated their opinions from . . . far-removed animal studies"); *see also, e.g.*, *In re TMI Litig.*, 193 F.3d at 683 (excluding several experts for lack of fit and noting that expert opinion must be excluded when it does not "reliably flow from the facts known to the expert and the methodology used") (citation omitted). Courts both within and outside the Third Circuit regularly apply this principle to bar purported expert testimony. *See, e.g.*, *Leake v. United States*, 843 F. Supp. 2d 554, 562 (E.D. Pa. 2011); *In re Human Tissue Prods. Liab. Litig.*, 582 F. Supp. 2d 644, 666-67, 670, 672 (D.N.J.

2008); *In re Rezulin*, 369 F. Supp. 2d at 426, 428-35. In particular, courts have repeatedly excluded supposed experts who leap from evidence of one biological phenomenon to a causal conclusion; they have also repeatedly barred experts who rely on in vitro or animal studies to demonstrate reactions in humans, unless the experts are able to reliably "bridge the gap" between their data and their conclusion. *Leake*, 843 F. Supp. 2d at 562-63.

Here, Dr. Saed did not bridge the gap – ***by his own admission***. Specifically: (1) he admitted that he needed to – but did not – conduct animal studies to confirm that his petri dish findings faithfully replicate what would happen in vivo; and (2) even his conclusions about what he found in his petri dishes are not supported by the data his experiment generated.

A. Even If Dr. Saed Had Demonstrated Carcinogenesis In Vitro, That Would Not Establish A Mechanism of Carcinogenesis In Vivo, Much Less In Human Beings.

As courts have repeatedly recognized, in vitro "studies are not as helpful as either epidemiological or animal studies because they are conducted outside of a biological environment, and the conclusions of these studies will always remain one step removed from directly proving causation." *In re Human Tissue*, 582 F. Supp. 2d at 663; *see also In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1294-95 (M.D. Fla. 2007) ("'The problem with [the in vitro] approach is . . . extrapolation—whether one can generalize the findings from the artificial setting

of tissues in laboratories to whole human beings.' That is, studies such as these necessarily remove the cells from the dynamic metabolic context in which the human body actually processes chemical compounds.") (quoting Green et al., Fed. Jud. Ctr., *Reference Guide on Epidemiology*, in *Reference Manual on Scientific Evidence* 333, 346 (2d ed. 2000)); *Wade-Greaux*, 874 F. Supp. at 1454, 1484. As such, while in vitro studies are not categorically inadmissible, they should only be admitted where the expert can explain why the in vitro media used for the studies "are similar or duplicate the human tissue environment." *In re Human Tissue*, 582 F. Supp. 2d at 670; *see Wade-Greaux*, 874 F. Supp. at 1484 (explaining that "[w]hile *in vitro* and *in vivo* animal studies can be helpful," data derived from such studies "are not relied upon by experts . . . for extrapolating the results found directly to the human experience").

Dr. Saed offered no such explanation; indeed, he stated the opposite: "to simulate with what's on [sic] in vivo, ***you have to do animal studies***,"[140] and an "[i]n vitro model is a good predictor to determine whether a substance is carcinogenic or not" ***only "if the same effect is replicated in vivo."***[141] Dr. Saed also acknowledged that he is not aware of ***any*** substance that has ever been

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140 (Saed 2/14/19 Dep. 542:20-21 (emphasis added).)

141 (Saed 1/23/19 Dep. 333:7-9 (emphasis added).)

classified as a carcinogen on the basis of in vitro studies alone.[142] Notably, this is consistent with one of the comments provided to Dr. Saed when his submission to *Gynecologic Oncology* was rejected. (*See* Rejection Letter at 2 ("The significance of this study would be greatly enhanced if a mouse model corroborated the cell line findings. In this reviewer's opinion the cell line studies alone . . . are not sufficiently convincing.").)[143]

Critically, Dr. Saed did not offer any good reason for his failure to conduct an animal study; instead, when asked, he said he "just do[es]n't have the time to do it and the money."[144] But that limitation does not excuse him from following universally accepted scientific principles. *Wessmann v. Gittens*, 160 F.3d 790, 805 (1st Cir. 1998) ("The only excuse that Dr. Trent proffered for his failure to follow proper protocols was that a thorough study would have required more time than he had available. That is unacceptable.").

Perhaps attempting to compensate for this fact, Dr. Saed contended at his deposition that his position was supported by animal studies conducted by others. But when repeatedly pressed to name any published literature, the only study he

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142 (*See id.* 333:2-4.)

143 Of course, animal studies have their own limitations that would have to be accounted for in any future study. *See, e.g.*, *Soldo*, 244 F. Supp. 2d at 547 (excluding experts who relied on animal studies for "failure to take into account critical differences between animal data and human experience").

144 (Saed 1/23/19 Dep. 50:10-13.)

could remember was a rat study by the National Toxicology Program, and he could not recall whether that study even found an association between talcum powder and ovarian cancer.[145] It did not.[146] Dr. Saed's report relatedly contends that "[s]tudies that exposed lab animals (rats, mice, and hamsters) to asbestos-free talcum powder in various ways have had mixed results."[147] But the two studies that he cites for this proposition have nothing to do with talcum powder, and one of them has nothing to do with animals.[148] The first, Graham & Graham (1967), did show some biological changes in rabbits and guinea pigs (though not in hamsters or mice), but after injection of ***tremolite asbestos,*** not talc.[149] The other cited paper, Langseth & Kjaerheim (2004), is even further afield. This was an epidemiological study of human exposure, not an experiment performed on animals, and, in any event, it plainly undercuts Dr. Saed's position rather than supports it, because it concluded that "[t]he results ***do not confirm*** an association

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145 (*See* Saed 1/23/19 Dep. 191:6-196:11.)

146 (Expert Report of Michael Birrer, M.D., Ph.D. ("Birrer Rep.") at 17, Feb. 25, 2019 (attached as Ex. C33 to Tersigni Cert.) (noting with respect to the NTP study that there was no greater incidence of ovarian cancer in talc-exposed rats compared to controls).)

147 (Saed Rep. at 10.)

148 (*See id.* at 27 nn.50-51.)

149 Graham & Graham, *Ovarian cancer and asbestos*, 1 Envtl Res. 115 (1967) (attached as Ex. A49 to Tersigni Cert.) (cited in Saed Rep. at 27 n.50).

between exposure to asbestos [or] talc . . . and ovarian cancer . . . ."[150] Dr. Saed's attempt to draw conclusions from articles that the articles themselves do not support – and in one case expressly rejects – is plainly not reliable. *See, e.g.*, *In re Mirena (No. II)*, 341 F. Supp. 3d at 241 ("[W]hen an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study.") (quoting *In re Accutane Prods. Liab.*, No. 8:04-md-2523-T-30TBM, 2009 WL 2496444, at *2 (M.D. Fla. Aug. 11, 2009), *aff'd*, 378 F. App'x 929 (11th Cir. 2010) (per curiam)) (alteration in original).

Finally, the gap between Dr. Saed's in vitro experiments and the causal conclusion he sought to support was even wider due to the dose issues noted above. To extrapolate from laboratory findings, an expert must either show that he used a similar dosage or else that the dosage used is otherwise relevant to human exposure scenarios. *See In re Rezulin*, 369 F. Supp. 2d at 430-31 ("[I]f the doses at which Rezulin was observed to be toxic to cultured cells are not achieved in the liver *in vivo*, extrapolation from the *in vitro* experiments is not reliable."); *Soldo*, 244 F. Supp. 2d at 485 (rejecting "animal studies" in which "doses of bromocriptine vastly [exceed] those used" in human treatment and in vitro studies

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150 *See* Langseth & Kjaerheim, *Ovarian cancer and occupational exposure among pulp and paper employees in Norway*, 30(5) Scandinavian J. Work Envtl Health 356 (2004) (attached as Ex. A87 to Tersigni Cert.) (cited in Saed Rep. at 11 & 27 n.51) (emphasis added).

in which "enormous doses of bromocriptine were injected"). But as already shown, even Dr. Saed had to agree that the amount of talc he used in his experiments "definitely . . . does not correlate with the *in vivo* and how much you will get with that exposure."[151] Thus, even if it were possible to premise causal conclusions on some in vitro studies, Dr. Saed's study would not be one of them.

In short, there is too great a gap between Dr. Saed's study and the conclusion that he has established a biological mechanism of cancer – as accepted science makes plain and Dr. Saed's own admitted need to conduct animal studies confirms. For this reason, too, his opinions are unreliable and should be excluded.

B. The Biological Effects Dr. Saed Reportedly Found In His Study Do Not Support The Conclusion That Talc Is A Carcinogen.

Leaving aside Dr. Saed's failure to conduct an animal study, the data he reports from his study do not support any carcinogenic effect of talc. Indeed, both reviewers at *Gynecologic Oncology* agreed, the first writing that Dr. Saed's claim that "'[o]xidative stress is a key mechanism to the initiation and progression of ovarian cancer' is not supported by this investigation" and the second similarly objecting that "the present data are insufficient to back up the claim that talcum is central to the development of ovarian cancer."[152]

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151 (Saed 1/23/19 Dep. 233:11-234:1.)

152 (Rejection Letter at 2 (citation omitted).)

It is well established that experts cannot extrapolate injury from an observed biological change unless they have "evidence to carry them all the way down their causal chain" to their ultimate conclusion. *In re Rezulin*, 369 F. Supp. 2d at 427; *see also, e.g.*, *Leake*, 843 F. Supp. 2d at 562 (excluding experts because they could not demonstrate that "binding of [chemical] to proteins and DNA" could cause "'protein adducts' and an 'immune-mediated' reaction resulting in liver failure"). Thus, where experts jump from biological effects in petri dishes to grand conclusions about causation without providing scientific evidence linking the two, courts routinely exclude their opinions as unreliable.

In *Rezulin*, for example, the court excluded a series of general causation experts who sought to opine on a biological mechanism by which Rezulin, a diabetes medication, could cause so-called silent liver injury – i.e., liver injury without the typical corresponding increase in liver enzyme blood levels. One of plaintiffs' experts' theories was that "(a) Rezulin has been shown to affect the structure and function of the mitochondria, and (b) apoptosis has been shown to involve changes to the mitochondria, and therefore (c) Rezulin can produce apoptosis." 369 F. Supp. 2d at 427. Apoptosis, in turn, according to plaintiffs' experts, could cause silent liver damage. *See id.* at 410.

The court rejected these opinions under *Daubert*, explaining that the leap from the data regarding Rezulin's effect on mitochondria to the conclusion that

Rezulin could induce apoptosis was "logically equivalent to saying that (a) every time John gets hungry he eats, and (b) John eats whenever he goes to a restaurant, therefore (c) every time John gets hungry, he goes to a restaurant." *Id.* at 427. "[O]f course," the court went on, there are "plenty of times when John gets hungry and eats at home." *Id.* The *Rezulin* court independently rejected the experts' extrapolation for the additional reason that even if the drug did induce apoptosis, that conclusion was insufficient to establish a reliable link to silent liver injury, in large part because "some level of apoptosis is entirely normal and occurs all the time in healthy tissue." *Id*. In short, although the data on which the experts relied might have been ***consistent*** with the conclusions that they drew from them, the experts could not complete the causal chain from data to conclusions because the data were also consistent with a contrary conclusion. *Id*. As the court explained, while "investigation of the molecular mechanisms" of disease might be "promising and potentially clinically relevant . . . 'the courtroom is not the place for scientific guesswork, even of the inspired sort.'" *Id.* at 438 (quoting *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996)).

Here, Dr. Saed's opinions are similarly unreliable and inadmissible because: (1) his data do not support the conclusion that talc promotes transformation of normal cells to cancer cells; (2) his premise that oxidative stress or inflammation is relevant to ovarian cancer is unsubstantiated and, in any event, his data do not

support the conclusion that talc contributes to either process; (3) his data regarding SNPs do not support the conclusion that talc causes mutations relevant to ovarian cancer; and (4) his claimed finding of elevated CA-125 levels is meaningless.

1. None Of Dr. Saed's Data Support The Conclusion That Talc Causes Normal Cells To Transform Into Cancer Cells.

First, none of Dr. Saed's findings support his conclusion that "Johnson's Baby Powder exposure can cause ovarian cancer."[153] As Dr. Saed himself put it before he began his work, "***neoplastic transformation of [normal] cells over time . . . is critical in establishing a cause and effect relationship***."[154] But he did not test for that. As one of the *Gynecologic Oncology* reviewers expressly put it, Dr. Saed's "data do not show, despite the authors' claim, any evidence that these cells were transformed."[155] Notably, Dr. Saed did not dispute this conclusion at his deposition; while he blamed the absence of evidence of transformation on the fact that his tests were run on immortalized cells, he had to agree that his cells did "not transform."[156]

Dr. Saed nevertheless insisted that he had provided other evidence of transformation through evidence of increased cell proliferation, which he described

153 (Saed Rep. at 20.)

154 (Proposal at 3.)

155 (Rejection Letter at 2.)

156 (Saed 2/14/19 Dep. 464:13-17.)

with a mouthful of caveats as "an indirect measure of – of the beginning of a transformation."[157] The indirectness of Dr. Saed's measure makes it insufficient to support his conclusion because, as in *Rezulin*, the results are at best consistent with – and not remotely conclusive of – carcinogenic effect. Cell proliferation is not the same thing as neoplastic transformation; rather, as Dr. Saed admitted at his deposition, proliferation is "a normal response of all normal cells to agents."[158] And Dr. Saed could not point to a single study linking cell proliferation with the development of cancer of any kind, much less with the development of ovarian cancer.[159]

In short, as in *Rezulin*, the indirect measure on which Dr. Saed relies is also "entirely normal and occurs all the time in healthy tissue," 369 F. Supp. 2d at 427; thus, his alleged observation of enhanced proliferation does not support any conclusions about carcinogenesis.

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157 (*Id.* 464:5-11.)

158 (Saed 1/23/19 Dep. 265:12-17.)

159 (*Id.* 268:10-269:4 (THE WITNESS: "Okay, so you're asking if there are reports showing that there is the increased proliferation is associated [sic] with increased cancer risk?" . . . Q. "Correct." A. "Okay, again, I'm answering, the answer is I don't know . . . .").)

2. Dr. Saed's Premise That Oxidative Stress Or Inflammation Are Relevant To Ovarian Carcinogenesis Is Unsubstantiated, And His Data In Any Event Do Not Prove An Increase In Either.

Dr. Saed's conclusions regarding oxidative stress and inflammation likewise do not support his causation opinion, for multiple reasons.

First, Dr. Saed's basic premise – that oxidative stress or inflammation have anything to do with ovarian carcinogenesis[160] – is unsubstantiated.[161] As Dr. Saed himself acknowledges, reactive oxygen species (or "ROS") "are part of normal cell physiology" at "normal levels."[162] For this reason, one of the reviewers for *Gynecologic Oncology* criticized Dr. Saed's claim that "'[o]xidative stress is a key mechanism in the initiation and progression of ovarian cancer,'" noting that this claim "is not supported by this investigation and should be omitted."[163]

In an effort to link altered ROS levels to ovarian cancer, Dr. Saed resorts to misrepresenting the published literature – some of it his own. For example, in support of his contention that ovarian cancer has "been strongly associated with . . . oxidative stress," he cites to a single article by Reuter et al. (2010), which does not

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160 (Saed Rep. at 4-5, 20.)

161 (*See generally* Memorandum Of Law In Supp. Of Mot. To Exclude Pls.' Experts' Ops. Related To Biological Plausibility at 48-65.)

162 (Saed Dep. 1/23/19 299:24-25.)

163 (Rejection Letter at 2 ("[w]hile changes in redox potential[ly] play an important role in tumor biology in general, the present data are insufficient to back up the claim that talcum is central to the development of ovarian cancer").)

mention ovarian carcinogenesis a single time.[164] Dr. Saed also attempts to bolster his related contention that "recent evidence suggests that oxidative stress is a critical factor in the initiation and development of . . . ovarian cancer," with citation to two studies – one for which he was lead author – that have nothing to do with cancer initiation.[165] And Dr. Saed's assumptions regarding inflammation are similarly unsupported and flawed because, as set forth in greater detail in defendants' motion to exclude plaintiffs' experts' biological plausibility opinions, the available evidence suggests that inflammation like oxidative stress is at most an effect, rather than a cause, of ovarian cancer.[166] In short, Dr. Saed confuses "association with causation," *In re Rezulin*, 369 F. Supp. 2d at 427, a methodological flaw that renders his opinions all the more inadmissible.

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[164] *See* Reuter et al., *Oxidative Stress, Inflammation and Cancer: How Are They Linked?* 49 Free Radical Bio. Med. 1603 (2010) (attached as Ex. A120 to Tersigni Cert.) (cited in Saed Rep. at 4 & 22 n.5).

[165] *See* Saed et al., *Dichloroacetate Induces Apoptosis of Epithelial Ovarian Cancer Cells Through a Mechanism Involving Modulation of Oxidative Stress*, 18 Reprod. Sci. 1253 (2011) (attached as Ex. A127 to Tersigni Cert.) (cited in Saed Rep. at 5 n.12) (testing the effect of oxidative stress treatment on cancer cells); Senthil et al., *Evidence of Oxidative Stress in the Circulation of Ovarian Cancer Patients*, 339 Clinica Chimica Acta 27 (2004) (attached as Ex. A130 to Tersigni Cert.) (cited in Saed Rep. at 5 & 23 n.14) (testing oxidative stress levels among ovarian cancer patients).

[166] (*See* Memorandum Of Law In Supp. Of Mot. To Exclude Pls.' Experts' Ops. Related To Biological Plausibility at 57-58.)

Second, Dr. Saed's data do not establish that talc increases oxidative stress. While he purports to have found alterations in certain enzymes associated with pro- and anti-oxidant properties, there is no evidence that the net result of these alleged changes in isolated enzymes would alter the redox balance in vivo. Instead, Dr. Saed chose to measure redox "indirectly" and inferred from that measurement that talc promotes a pro-oxidant environment.[167]

But Dr. Saed's decision to rely on indirect, rather than direct, measurements again saps his findings of any value in supporting his sweeping causation conclusions. As Dr. Saed himself acknowledged, "[o]xidative stress is a balance" and "not just [a] simple process,"[168] underscoring the unreliability of relying on claimed changes in activity of isolated enzymes. Notably, there are multiple standardized measurements that Dr. Saed and his colleagues could have employed to measure ROS.[169] Indeed, Dr. Saed acknowledged this, agreeing at his deposition that other measures exist, while lamenting that it is "[v]ery difficult" to measure intracellular redox directly and asserting that the "data will not be very

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167 (Saed 1/23/19 Dep. 306:21-307:24.)

168 (*Id.* 304:7-10.)

169 (*See* Neel Rep. at 22.)

reliable."[170] But Dr. Saed offered no evidence for this conclusion or any other explanation for his failure to use a more direct measure of intracellular redox.[171]

Because Dr. Saed declined to perform direct tests that may have demonstrated or refuted his hypothesis that talc induces oxidative stress, his conclusions on the altered redox balance are also unreliable.

Third, Dr. Saed's conclusion that "Johnson's Baby Powder elicits an inflammatory response . . . that can result in the development and the progression of ovarian cancer"[172] is, if anything, even more unsupported. After all, Dr. Saed ***did not even measure inflammation***.[173] Nor could he cite any literature suggesting that perineal talc use causes inflammation; rather, when asked that very question, he responded that he "do[es]n't know any references."[174] To the extent Dr. Saed intends to suggest that inflammation is the same as, is caused by, or contributes to

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170 (Saed 1/23/19 Dep. 306:21-307:7.)

171 Moreover, even his indirect measures failed to uniformly show decreases in anti-oxidant levels with talc treatment, further deepening the gulf between his data and the conclusions he attempts to draw from them. (*See* Saed 2/14/19 Dep. 411:1-412:6.)

172 (Saed Rep. at 20.)

173 Dr. Saed claims that CA-125 is a "marker of inflammation" (Saed 1/23/19 Dep. 248:18-19), but his CA-125 findings are irrelevant for the reasons discussed in subsection 4, below.

174 (*Id.* 172:23.)

alterations in the redox balance,[175] his inflammation claims lack support for the same reasons the oxidative stress conclusions do.[176]

In short, Dr. Saed's conclusions about oxidative stress and inflammation are not supported by the admittedly "indirect" measures he employed, and in any event rest on an unproven premise about the hypothesized relationship between oxidative stress or inflammation and ovarian cancer (the very relationship he needed to prove to support his opinions). For this reason, too, his opinions are unreliable and inadmissible.

3. Dr. Saed's Claimed SNP Findings Prove Nothing Because No Scientific Data Link The Changes He Reports To Ovarian Cancer.

Dr. Saed's claim "that talc treatment induced gene point mutations that happen to" code for certain redox enzymes "such as *CAT*, *GPX1*, *GSR*, and *SOD2*," even if true, also does not support his conclusion that talc causes ovarian cancer, for several reasons.

Most fundamentally, even if Dr. Saed had identified talc-induced mutations, he offers no reason to link them to ovarian cancer. It is axiomatic that many SNPs,

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175 (*See, e.g.*, *id.* 239:20-240:2.)

176 Dr. Saed's conclusion that talc has anything to do with the progression of ovarian cancer is completely unsupported. When asked about the basis for this opinion at his deposition, he could only refer in a conclusory fashion to his alleged findings concerning oxidative stress, without explaining why he believes that the mechanisms for the initiation and progression of ovarian cancer would be identical. (*See id.* 246:19-247:19.)

and genetic mutations generally, are "silent" – i.e., they have no effect on the coding of proteins at all.[177] As Dr. Saed acknowledged at his deposition, to identify which mutations are potentially involved in tumor development, scientists engage in genome-wide association studies ("GWAS").[178] Dr. Saed himself identifies some such SNPs that have been correlated with ovarian cancer risk in his report.[179] But these mutations are ***not*** examined by his study.

Instead, Dr. Saed's experiment examines other SNPs – ***none*** of which is among those he listed as related to ovarian cancer. Specifically, Dr. Saed relies on alleged findings of specific mutations (rs769217, rs2297518 , rs8190955, rs3448 and rs2536512) in redox genes to support his theory that the perineal application of talc may increase ovarian cancer risk in humans. But he does not cite a single study showing that any of these mutations has a genome-wide significance for association with ovarian cancer risk. Defense experts have confirmed that none of them has been identified as having genome-wide significance for an association with ovarian cancer risk.[180]

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177 (*See* Boyd Rep. at 13.)

178 (Saed 2/14/19 Dep. 530:2-9.)

179 (*See* Saed Rep. at 8 (identifying various SNPs – rs1001179, rs4673 and rs2333227 – associated with ovarian cancer).)

180 (*See* Boyd Rep. at 12-13; Shih Rep. at 6-7.)

Dr. Saed resisted this conclusion at his deposition, but he could not substantiate his protests. He claimed that his lab had established that a catalase SNP is associated with ovarian cancer,[181] but in doing so, he mischaracterized the findings of his own study, which "found an association between a specific SNP in the *CAT* gene and ovarian cancer ***survival***, not risk,"[182] as Dr. Saed ultimately had to conclude after re-reading the article at his deposition.[183] Dr. Saed also contended that a myeloperoxidase SNP "has been associated with ovarian cancer," but when asked whether the SNP has achieved genome-wide significance, he could respond only, "I don't know."[184]

This failure to cite studies demonstrating the significance of mutations that Dr. Saed examined in his study and his reliance on studies completely unrelated to these mutations "is contrary to methods accepted by the scientific community." *See Rutigliano v. Valley Bus. Forms*, 929 F. Supp. 779, 784-85 (D.N.J. 1996) (excluding plaintiff's expert's opinions in part because "credentialed allergists or immunologists" would not "rely upon data extrapolated from articles to support

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181 (Saed 1/23/19 Dep. 211:6-212:10.)

182 (Boyd Rep. at 12.)

183 (*See* Saed 1/23/19 Dep. 218:11-14 (conceding, after several pages of questioning forcing the issue, that "yeah, so this here we only did analysis of survival").)

184 (Saed 2/14/19 Dep. 531:15-532:8.)

conclusions not drawn by the articles' authors"). For this reason, too, his opinions are unreliable and should be excluded.

4. Dr. Saed's CA-125 Findings, Even If Correct, Have No Relevance To Ovarian Carcinogenesis.

Finally, Dr. Saed's claim that he observed elevated levels of CA-125[185] also cannot support a sweeping conclusion about ovarian cancer.

As explained above, CA-125 is a blood serum marker that is correlated with ovarian cancer progression and treatment response but has generally been deemed insufficiently sensitive or specific to serve as a reliable indicator of risk for ovarian cancer. As Dr. Saed acknowledged at his deposition, CA-125 is "not specific to ovarian cancer."[186] Dr. Saed also admitted that he does not know whether CA-125 has any significance in diagnosing ovarian cancer or determining its cause.[187]

In fact, while CA-125 can be elevated in ovarian cancer patients, it is also elevated in response to many other conditions – including endometriosis, pregnancy, ovulatory cycles, liver disease, congestive heart failure and tuberculosis – and increased levels of CA-125 in vivo usually ***do not*** indicate ovarian cancer.[188] Given this range of associations and other issues, "the

185 (Saed Rep. at 18.)

186 (Saed 1/23/19 Dep 248:3.)

187 (*Id.* 248:9-249:12.)

188 (Boyd Rep. at 9.)

specificity and sensitivity of serum CA-125 levels are unacceptably low" for purposes of ascertaining ovarian cancer risk.[189] Moreover, as Dr. Neel explains, CA-125 "has no known role in ovarian cancer *causation*"; thus, "[w]hether or not talc induces CA-125 expression says nothing about talc having any carcinogenic effect."[190] Thus, Dr. Saed's effort to link this protein with cancer causation "is speculative, and it confuses association with causation." *In re Rezulin*, 369 F. Supp. 2d at 427.[191]

In his manuscript, Dr. Saed seemingly tries to bridge this gap by contending that CA-125 induces inflammation.[192] But his contention that CA-125 causes or is indicative of inflammation that could have any relevance to ovarian cancer is pulled out of thin air and unsupported by any citation. And while Dr. Saed attempted an explanation at his deposition, he could not answer the straightforward question whether CA-125 is associated with inflammation in women who have not

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189 (*Id.*)

190 (Neel Rep. at 26.)

191 (*Accord* Birrer Rep. at 20 ("The fact that CA-125 can be elevated in cases of ovarian cancer does not mean it can contribute to cancer causation. To take a simple example, a fever may be a 'biomarker' for a bacterial or viral infection, but the fever obviously does not contribute to causing the infection.").)

192 (Reproductive Sciences Manuscript at 2 (abstract) (discussing "inflammation as determined by increased . . . CA-125").)

been diagnosed with ovarian cancer.[193] In short, the elevated CA-125 levels reported in Dr. Saed's study are connected to a risk of ovarian cancer only by Dr. Saed's speculative and uninformed ipse dixit.

For all of these reasons, Dr. Saed's results would not support a finding of carcinogenesis even if they were otherwise reliable.

III. THE PEER-REVIEW PROCESS SURROUNDING DR. SAED'S MANUSCRIPT FURTHER SUPPORTS EXCLUSION.

Finally, while defendants anticipate that plaintiffs will argue that Dr. Saed's findings should be accepted because his manuscript was peer-reviewed and published, the circumstances surrounding Dr. Saed's publication efforts only counsel further in favor of exclusion because he manipulated the peer-review process by not disclosing the fact that plaintiffs' counsel paid him to write his article.

In *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), the Supreme Court explained that "submission to the scrutiny of the scientific community is a component of 'good science,' in part because it increases the likelihood that substantive flaws in methodology will be detected." *Id.* at 591-93. But as Judge Lifland cautioned in *Rutigliano*, publication is by no means a "'sine

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193 (*See* Saed 1/23/19 Dep. 249:24-250:2 ("Q. CA-125 is not used to diagnose whether inflammation is going on in women who do not have ovarian cancer? A. Ask the OB-GYN oncologist") (objection omitted).)

qua non' of admissibility." 929 F. Supp. at 785. This is particularly so where there were evident irregularities in the peer-review process. *E.g.*, *Wade-Greaux*, 874 F. Supp. 1441 (noting expert's failure to disclose conflicts of interest in manuscripts, funding of study costs by plaintiffs' counsel, and misrepresentations in revised manuscripts). Here, there are at least two such significant irregularities, either one of which supports exclusion of Dr. Saed's work because it calls the objectivity of all of his work into doubt.

First, Dr. Saed misrepresented the nature of his funding to the journals to which he submitted his manuscript at every stage of the submission and review process. There is no question that misrepresentation of funding status bears on the meaningfulness of peer review and the reliability of the expert's methods. *See, e.g.*, *In re Garlock Sealing Techs., LLC*, 504 B.R. 71, 79 (Bankr. W.D.N.C. 2014) (finding expert's studies unreliable in part because "[t]he materials used in the studies were provided with funding by plaintiffs' attorneys, but that fact was not disclosed"). That is precisely what Dr. Saed did here. As explained above:

- When Dr. Saed submitted his manuscript to his first-choice journal, *Gynecologic Oncology*, he made ***no disclosure at all***, instead falsely stating that the "authors have no conflicts of interest to declare."
- After *Gynecologic Oncology* rejected his manuscript, Dr. Saed submitted it to his backup choice, *Reproductive Sciences*. This time, he included a disclosure that he had "acted as a consultant regarding this topic for a fee," but did not disclose the fact of his involvement in related litigation or the fact that lawyers had paid him to write the manuscript.

- After the inadequacies of this disclosure were brought up at his deposition, Dr. Saed revised the disclosure in the final, published version of his manuscript, noting his role "in the talcum powder litigation," but falsely stating under a new, separate "Funding" heading that the "author(s) received no financial support for the research, authorship, and/or publication of this article."

Every one of these deceptions is material. Defendants anticipate that plaintiffs will argue that Dr. Saed undid the damage of earlier incomplete or absent disclosures by including a full disclosure in the published manuscript. But as just shown, while Dr. Saed amended one disclosure, he made a new, false disclosure regarding funding for the article, which – as he testified – came from plaintiffs' counsel in an amount between $36,000 and $42,000.[194] Moreover, and in any event, it is simply wrong to argue that the misleading disclosures in the submitted drafts have no impact of the final result. As defendants' experts testified, transparency in funding is critically important to the peer-review process.[195] And in this case, Dr. Saed attempted to get through the front door at two separate journals by hiding the fact that his research was paid for by lawyers rather than neutral third parties. At best, this was an error of judgment on the part of Dr. Saed

194 (Saed 1/23/19 Dep. 33:22-34:9.)

195 (*E.g.*, Dep. of Ie-Ming Shih, M.D., Ph.D. ("Shih Dep.") 210:12-211:1, Mar. 6, 2019 (attached as Ex. B28 to Tersigni Cert.) (explaining from his experience on editorial boards that it is "important for the reviewers to judge whether there is any conflict of interest during the review process").)

that strongly suggests that he lacks the objectivity required to provide reliable conclusions in this Court.

Second, Dr. Saed's work was rejected by *Gynecologic Oncology* – a cancer journal with reviewers who presumably have expertise in the field – on many grounds that Dr. Saed did not correct before obtaining publication approval from *Reproductive Sciences*.

As noted above, a principal purpose of the peer-review process is to detect methodological flaws. *Daubert*, 509 U.S. at 593 ("[S]ubmission to the scrutiny of the scientific community is a component of 'good science,' in part because it increases the likelihood that substantive flaws in methodology will be detected."). When such flaws are detected, basic scientific integrity demands that they be corrected; otherwise, denying publication based on those flaws would serve no purpose.

Apart from adding findings from his MTT and cascade-3 assays to address the issues of proliferation and apoptosis,[196] Dr. Saed ignored the objections of the *Gynecologic Oncology* editors, including their objection to his claims that either oxidative stress or talc was central to the cause of ovarian cancer, their expressed confusion over his SNP findings, and their insistence that replication of his results

[196] For the reasons already discussed, this additional testing failed to meet the requirement that ***Dr. Saed himself*** had set in his Proposal for proving the alleged carcinogenicity of talc.

in animals would be necessary to support a causal conclusion.[197] More concerning still was Dr. Saed's attempt to address one reviewer's expressed "surpris[e]" that SNPs could be changed after "such short exposure to talcum."[198] As described previously, Dr. Saed simply changed all references to time of treatment in the manuscript from 48 hours to 72 hours – even in many of the figures he included in the original manuscript, retaining the same results with a new heading proclaiming 24 more hours of treatment.[199]

In short, nothing that happened here reflects "peer review" in the sense imagined by *Daubert*. Instead, the evidence suggests, at worst, fraud and at best, extreme disregard for scientific standards set by Dr. Saed's ***relevant*** peers – i.e., gynecologic oncologists. For these reasons, too, the Court should exclude Dr. Saed's opinions as unreliable.

CONCLUSION

For the foregoing reasons, the Court should exclude evidence of Dr. Saed's experiments, his manuscript and his opinions.

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197 (*See* Rejection Letter at 2.)

198 (*Id.* at 3.)

199 (*See* Mossman Rep. at 31.)

Dated: May 7, 2019

Respectfully submitted,

Susan M. Sharko
DRINKER BIDDLE & REATH LLP
600 Campus Drive
Florham Park, New Jersey 07932
Telephone: 973-549-7000
Facsimile: 973-360-9831
E-mail: susan.sharko@dbr.com

John H. Beisner
Jessica D. Miller
SKADDEN, ARPS, SLATE,
MEAGHER & FLOM LLP
1440 New York Avenue, N.W.
Washington, D.C. 20005
202-371-7000

Attorneys for Defendants Johnson & Johnson and Johnson & Johnson Consumer Inc.